Attachments

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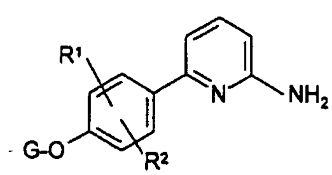
With international search report.

(54) Title: 2-AMINO-6-(2-SUBSTITUTED-4-PHENOXY)-SUBSTITUTED-PYRIDINES



(I)

(57) Abstract

This present invention relates to compounds of formula (I) wherein G, R^1 and R^2 are defined as in the specification that exhibit activity as nitric oxide synthase (NOS) inhibitors, to pharmaceutical compositions containing them and to their use in the treatment and prevention of central nervous system and other disorders.

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2-AMINO-6-(2-SUBSTITUTED-4-PHENOXY)-SUBSTITUTED-PYRIDINES

The present invention relates to certain 2-amino-6-(2-substituted-4-phenoxy)-substituted-pyridines that exhibit activity as nitric oxide synthase (NOS) inhibitors, to pharmaceutical compositions containing them and to their use in the treatment and prevention of central nervous system disorders, inflammatory disorders, septic shock and other disorders.

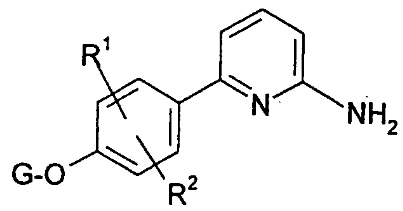
There are three known isoforms of NOS - an inducible form (I-NOS) and two constitutive forms referred to as, respectively, neuronal NOS (N-NOS) and endothelial NOS (E-NOS). Each of these enzymes carries out the conversion of arginine to citrulline while producing a molecule of nitric oxide (NO) in response to various stimuli. It is believed that excess nitric oxide (NO) production by NOS plays a role in the pathology of a number of disorders and conditions in mammals. For example, NO produced by I-NOS is thought to play a role in diseases that involve systemic hypotension such as toxic shock and therapy with certain cytokines. It has been shown that cancer patients treated with cytokines such as interleukin 1 (IL-1), interleukin 2 (IL-2) or tumor necrosis factor (TNF) suffer cytokine-induced shock and hypotension due to NO produced from macrophages, i.e., inducible NOS (I-NOS), see Chemical & Engineering News, Dec. 20, p. 33, (1993). I-NOS inhibitors can reverse this. It is also believed that I-NOS plays a role in the pathology of diseases of the central nervous system such as ischemia. For example, inhibition of I-NOS has been shown to ameliorate cerebral ischemic damage in rats, see Am. J. Physiol., **268**, p. R286 (1995)). Suppression of adjuvant induced arthritis by selective inhibition of I-NOS is reported in Eur. J. Pharmacol., **273**, p. 15-24 (1995).

NO produced by N-NOS is thought to play a role in diseases such as cerebral ischemia, pain, and opiate tolerance. For example, inhibition of N-NOS decreases infarct volume after proximal middle cerebral artery occlusion in the rat, see J. Cerebr. Blood Flow Metab., **14**, p. 924-929 (1994). N-NOS inhibition has also been shown to be effective in antinociception, as evidenced by activity in the late phase of the formalin-induced hindpaw licking and acetic acid-induced abdominal constriction assays, see Br. J. Pharmacol., **110**, p. 219-224 (1993). Finally, opioid withdrawal in rodents has been reported to be reduced by N-NOS inhibition, see Neuropsychopharmacol., **13**, p. 269-293 (1995).

Other NOS inhibitors and their utility as pharmaceutical agents in the treatment of CNS and other disorders are referred to in United States Provisional Application 60/032,793, filed December 6, 1996, and United States Provisional Application 60/014,343, filed March 29, 1996.

Summary of the Invention

This invention relates to compounds of the formula



I

wherein R^1 and R^2 are selected, independently, from hydrogen, halo, hydroxy, (C_1-C_6)alkoxy, (C_1-C_7)alkyl, (C_2-C_6)alkenyl, and (C_2 - C_{10})alkoxyalkyl; and

G is selected from hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_3)alkyl, aminocarbonyl-(C_1-C_3)alkyl-, (C_1-C_3) alkylaminocarbonyl -(C_1-C_3) alkyl-, di-[(C_1-C_3)alkyl]aminocarbonyl-(C_1-C_3)alkyl-, and $N(R^3)(R^4)$(C_0-C_4)alkyl-, wherein R^3 and R^4 are selected, independently, from hydrogen, (C_1-C_7) alkyl, tetrahydronaphthalene and aralkyl, wherein the aryl moiety of said aralkyl is phenyl or naphthyl and the alkyl moiety is straight or branched and contains from 1 to 6 carbon atoms, and wherein said (C_1-C_7) alkyl and said tetrahydronaphthalene and the aryl moiety of said aralkyl may optionally be substituted with from one to three substituents, preferably from zero to two substituents, that are selected, independently, from halo, nitro, hydroxy, cyano, amino, (C_1-C_4) alkoxy, and (C_1-C_4) alkylamino;

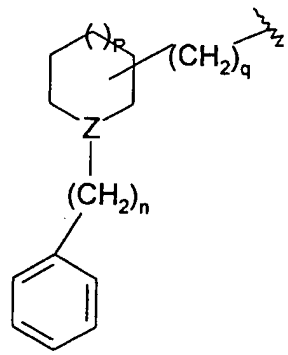
or R^3 and R^4 form, together with the nitrogen to which they are attached, a piperazine, piperidine, azetidine or pyrrolidine ring or a saturated or unsaturated azabicyclic ring system containing from 6 to 14 ring members, from 1 to 3 of which are nitrogen, from zero to two of which are oxygen, and the rest of which are carbon;

and wherein said piperazine, piperidine, azetidine and pyrrolidine rings and said azabicyclic ring systems may optionally be substituted with one or more substituents, preferably with from zero to two substituents, that are selected, independently, from (C_1-C_6)alkyl, amino, (C_1-C_6) alkylamino, [di-(C_1-C_6)alkyl]amino, phenyl substituted 5 to 6 membered heterocyclic rings containing from 1 to 4 ring nitrogen atoms, benzoyl, benzoylmethyl, benzylcarbonyl, phenylaminocarbonyl, phenylethyl and phenoxycarbonyl, and wherein the phenyl moieties of any of the foregoing substituents may optionally be substituted with one or more substituents, preferably with from zero to two substituents, that are selected, independently, from halo, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, nitro, amino, cyano, CF_3 and OCF_3;

and wherein said piperazine, piperidine, azetidine and pyrrolidine rings and said azabicyclic ring systems may be attached to -(C_0-C_4)alkyl-O- (wherein the oxygen of said -(C_0-

C_4)alkyl-O- is the oxygen atom depicted in structural formula I) at a nitrogen atom of the NR^3R^4 ring or at any other atom of such ring having an available bonding site;

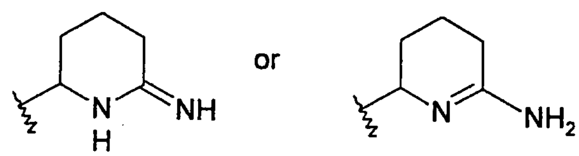
or G is a group of the formula A



(A)

wherein Z is nitrogen or CH, n is zero or one, q is zero, one, two or three and p is zero, one or two;

and wherein the 2-amino piperidine ring depicted in structure I above may optionally be replaced with



;

and the pharmaceutically acceptable salts of such compounds.

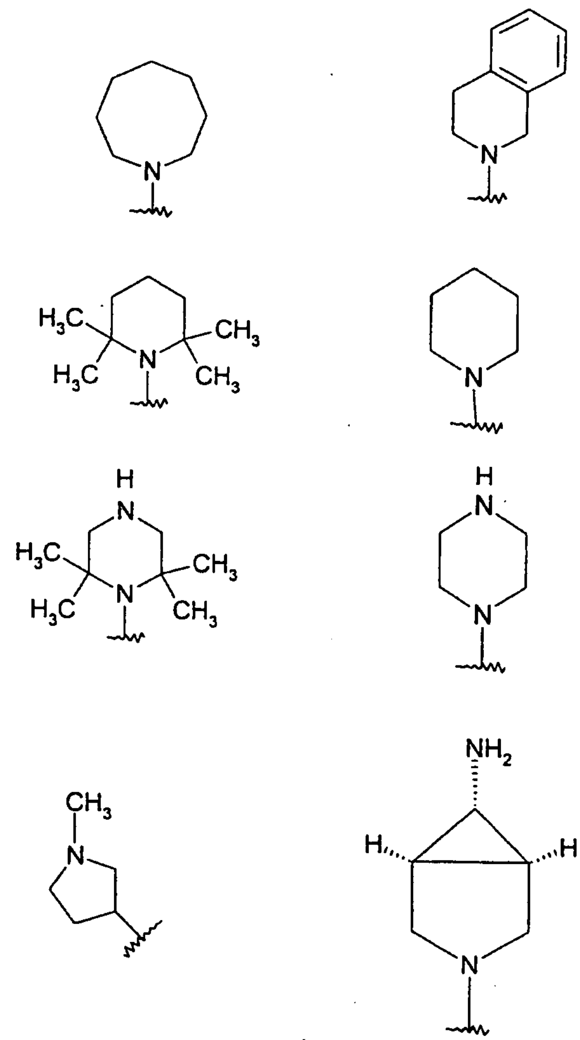
The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

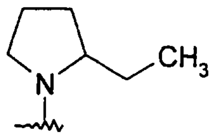
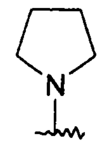
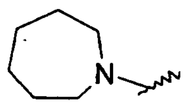
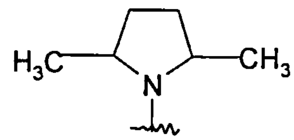
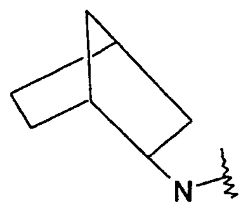
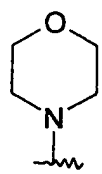
The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "one or more substituents", as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites.

The term "halo", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

Examples of compounds of this invention are compounds of the formula I, and their pharmaceutically acceptable salts, wherein G is $N(R^3)(R^4)(C_0\text{-}C_4)$ alkyl and $N(R^3)(R^4)$ is amino, dimethylamino, methylbenzylamino, $(C_1\text{-}C_4)$alkylamino, di-[$(C_1\text{-}C_4)$alkyl]amino or one of the following groups:



Preferred compounds of the formula I include those wherein R^2 is hydrogen and R^1 is $(C_1 - C_3)$alkoxy and is in the ortho position relative to the pyridine ring of formula I.

Other embodiments of this invention relate to compounds of the formula I wherein G is a group of the formula A, as defined above, wherein Z is nitrogen.

Other embodiments of this invention relate to compounds of the formula I wherein R^1 and R^2 are selected, independently, from $(C_1$-$C_2)$alkoxy.

Other embodiments of the invention relate to compounds of the formula I wherein G is a group of the formula A, as defined above, wherein Z is nitrogen, each of p and n is one and q is two.

Other embodiments of this invention relate to compounds of the formula I wherein the 2-aminopyridine ring depicted in formula I above, is present.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of migraine inflammatory diseases (e.g., asthma, psoriasis, eczema, arthritis) stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addiction (e.g., dependencies on drugs, alcohol and nicotine), emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury,

Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic nephropathy and cancer in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof that is effective in treating or preventing such condition, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a condition selected from the group consisting of migraine inflammatory diseases (e.g., asthma, psoriasis, eczema, arthritis), stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addictions (e.g., dependencies on drugs, alcohol and nicotine), emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic nephropathy and cancer in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such condition.

The present invention also relates to a pharmaceutical composition for inhibiting nitric oxide synthase (NOS) in a mammal, including a human, comprising an NOS inhibiting effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention also relates to a method of inhibiting NOS in a mammal, including a human, comprising administering to said mammal a NOS inhibiting effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of migraine, inflammatory diseases (e.g., asthma, psoriasis, arthritis, eczema), stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addictions (e.g., dependencies on drugs, alcohol and nicotine), emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic

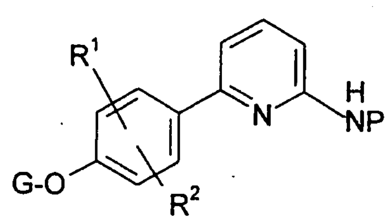
nephropathy and cancer in a mammal, including a human, comprising a NOS inhibiting effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a condition selected from the group consisting of migraine, inflammatory diseases (e.g., asthma, psoriasis, eczema, arthritis), stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addictions (e.g., dependencies on drugs, alcohol or nicotine), emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic nephropathy and cancer in a mammal, including a human, comprising administering to said mammal a NOS inhibiting effective amount of a compound of the formula II, or a pharmaceutically acceptable salt thereof.

Compounds of formula I have chiral centers and therefore may exist in different enantiomeric and diastereomeric forms. This invention relates to all optical isomers and all stereoisomers of compounds of the formula I and mixtures thereof, and to all pharmaceutical compositions and methods of treatment defined above that contain or employ them, respectively.

Formula I above includes compounds identical to those depicted but for the fact that one or more hydrogen, carbon or other atoms are replaced by isotopes thereof. Such compounds may be useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

This invention also relates to compounds of the formula



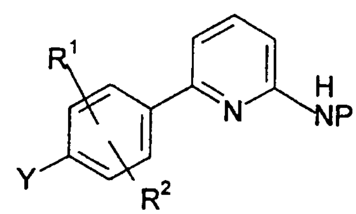
VIIA

wherein R^1, R^2 and G are defined as above for compounds of the formula I, and P is a nitrogen protecting group such as trityl, acetyl, benzoyl, trimethylacetyl, t-butoxycarbonyl, benzyloxycarbonyl, or another appropriate nitrogen protecting group, and wherein P can form

a ring with the protected nitrogen, in which case the hydrogen that is depicted above as being attached to such nitrogen is absent.

Such compounds are useful as intermediates in the synthesis of the pharmaceutically active compounds of formula I.

This invention also relates to compounds of the formula

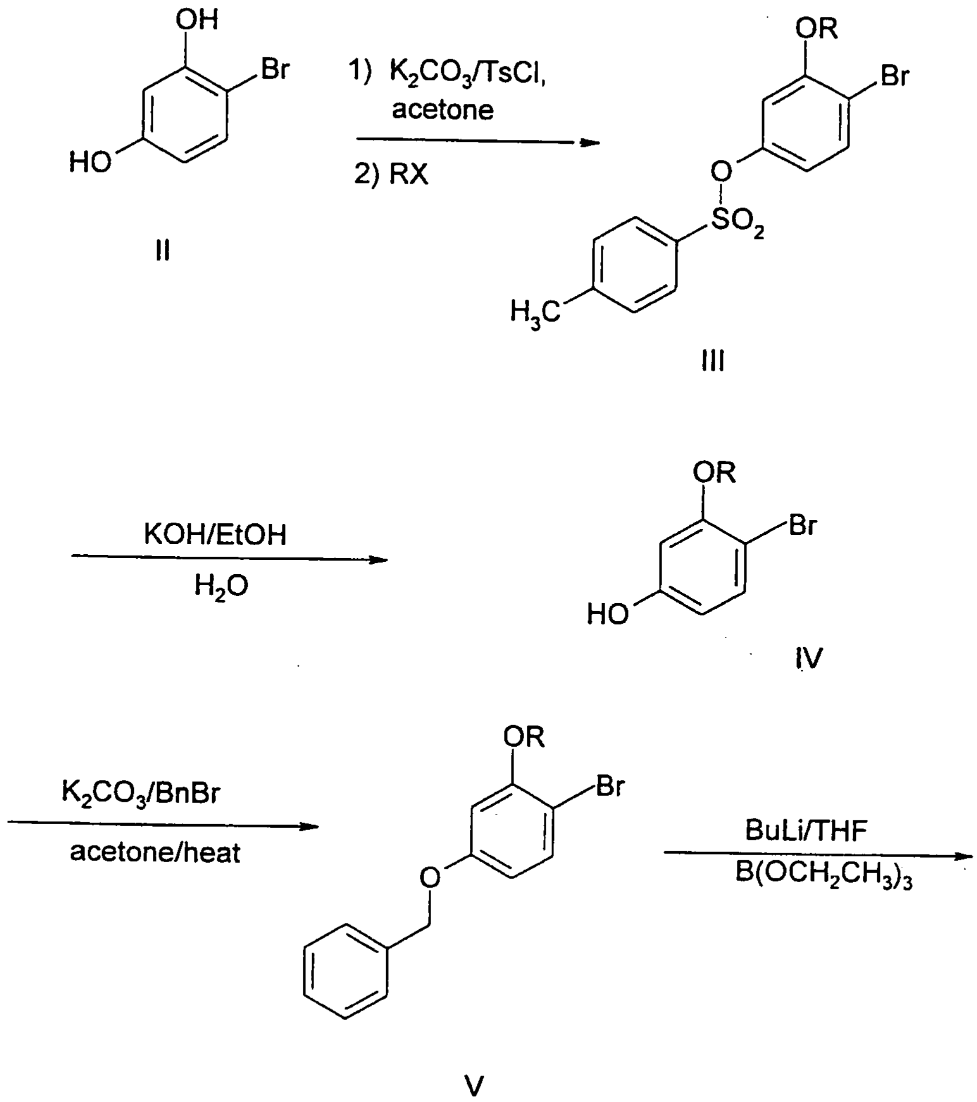


wherein R^1, R^2 and P are defined as above and Y is fluoro or benzyloxy. Such compounds are useful as intermediates in the synthesis of the pharmaceutically active compounds of formula I.

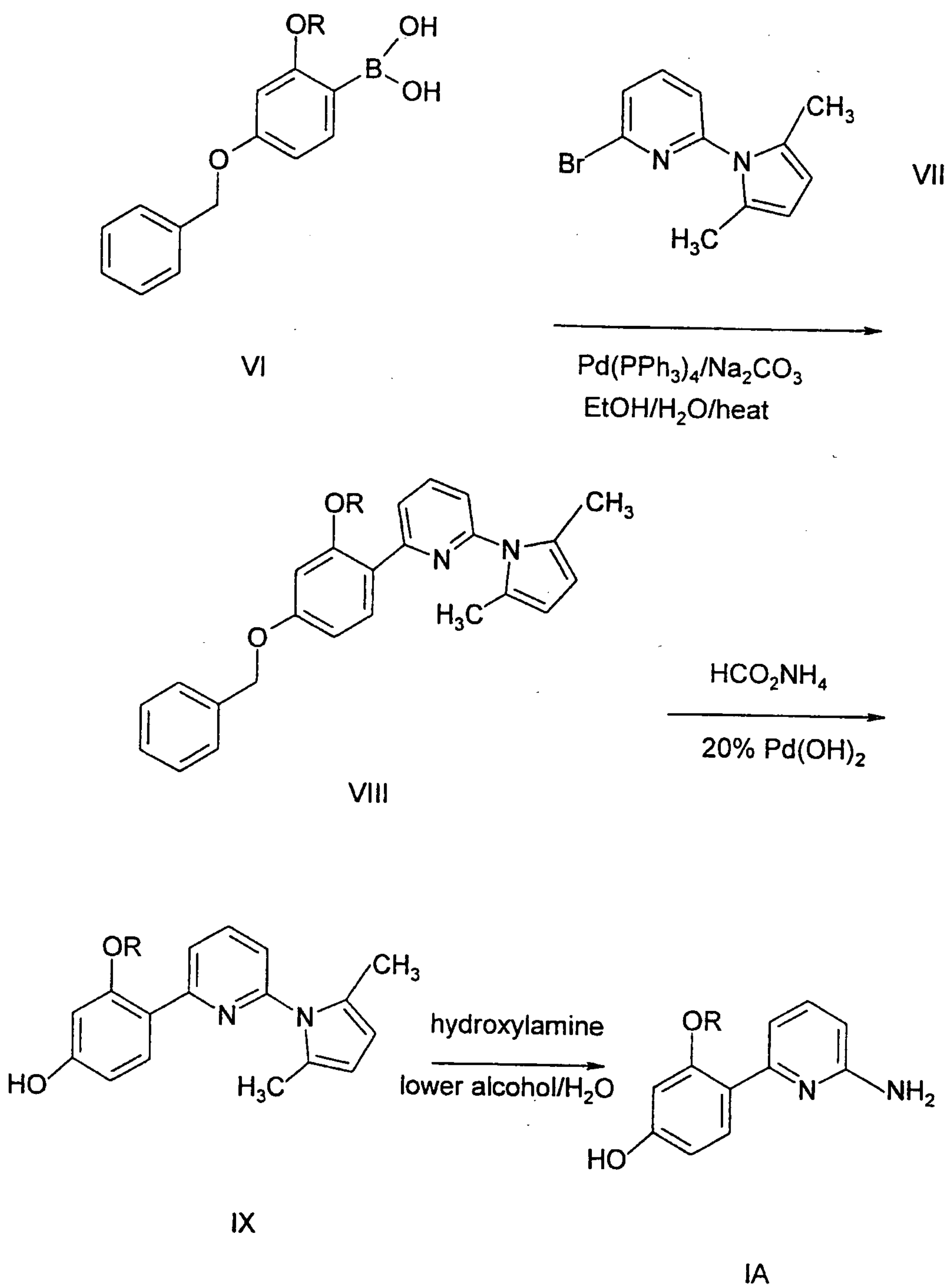
Detailed Description of the Invention

The compounds of the formula I may be prepared as described in the following reaction schemes and discussion. Unless otherwise indicated, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 and structural formula I in the reaction schemes and discussion that follow are defined as above.

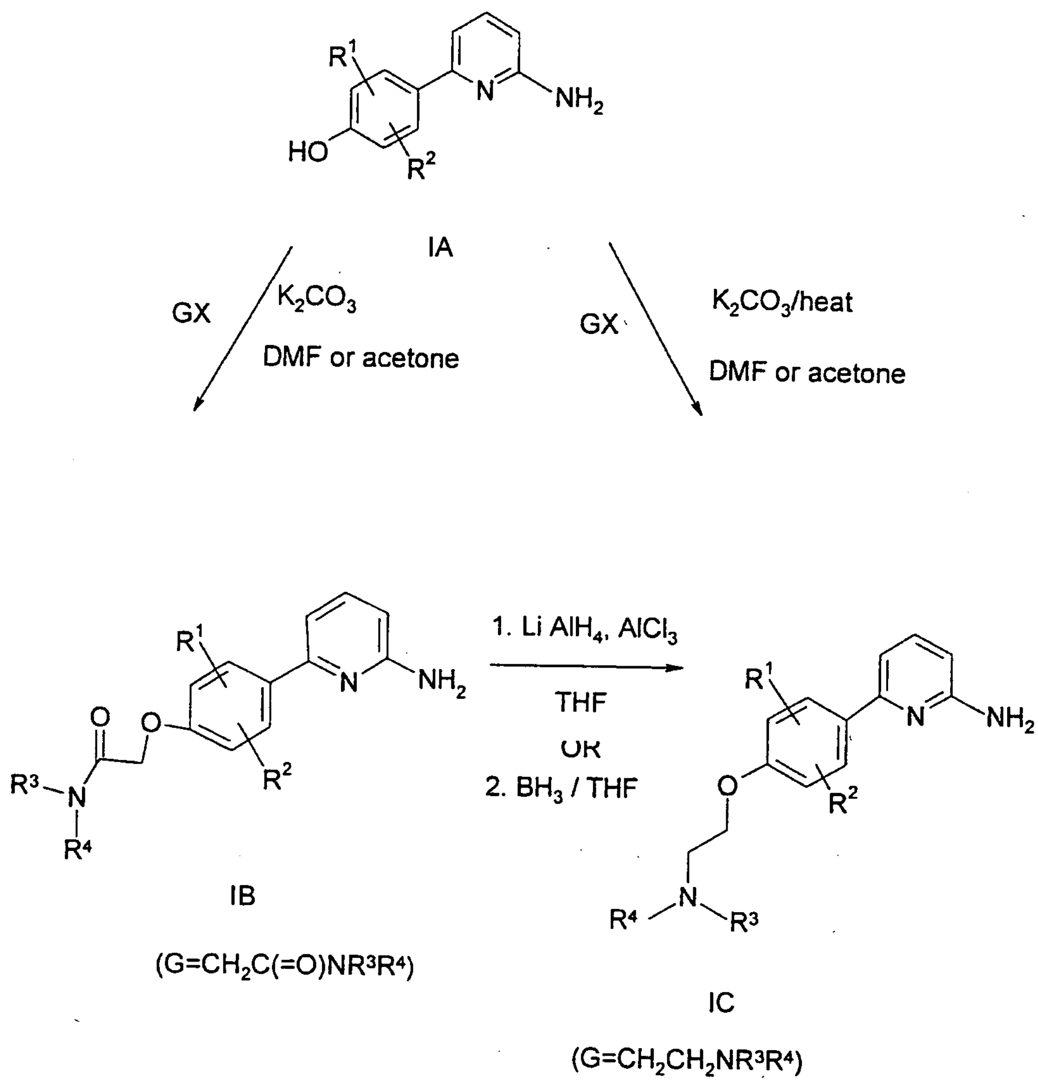
SCHEME 1


OH
Br
HO
II
1) K_2CO_3/TsCl, acetone
2) RX
OR
Br
O
SO_2
H_3C
III
KOH/EtOH
H_2O
OR
Br
HO
IV
K_2CO_3/BnBr
acetone/heat
OR
Br
O
V
BuLi/THF
$B(OCH_2CH_3)_3$

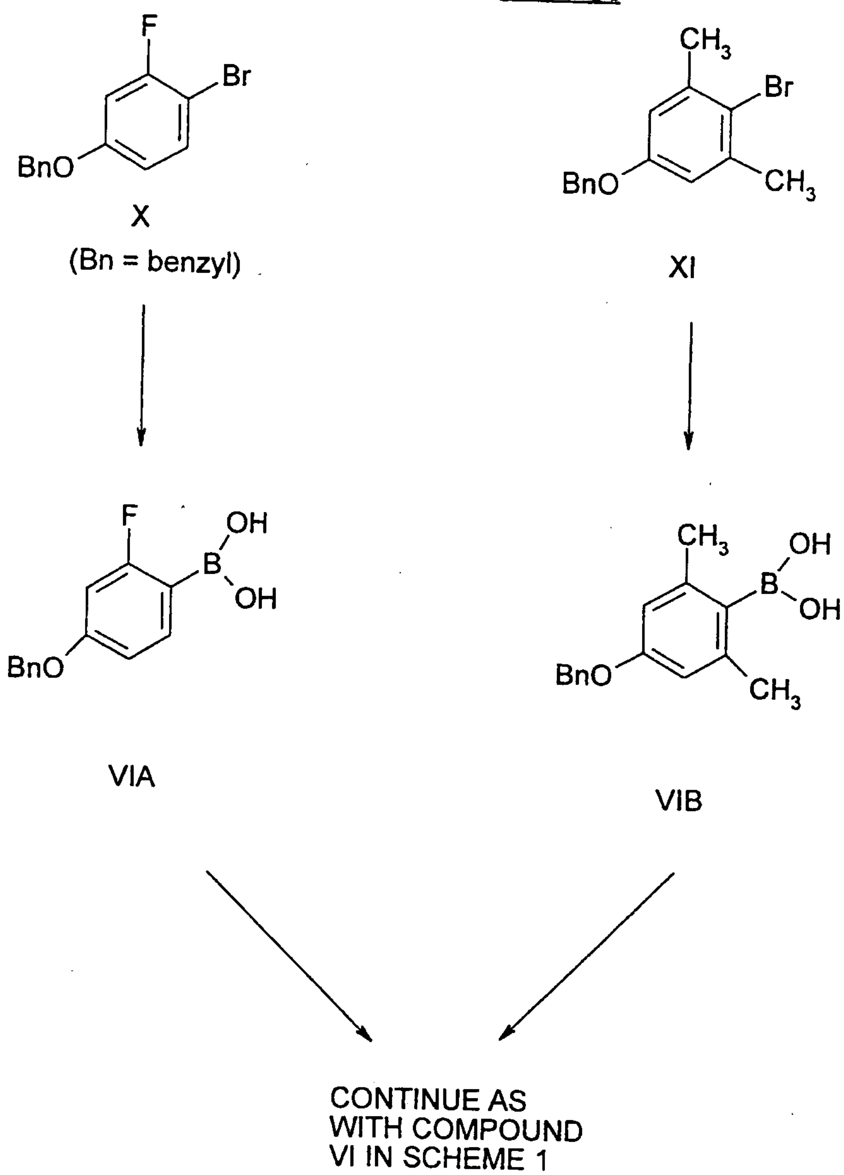
SCHEME 1 CONTINUED



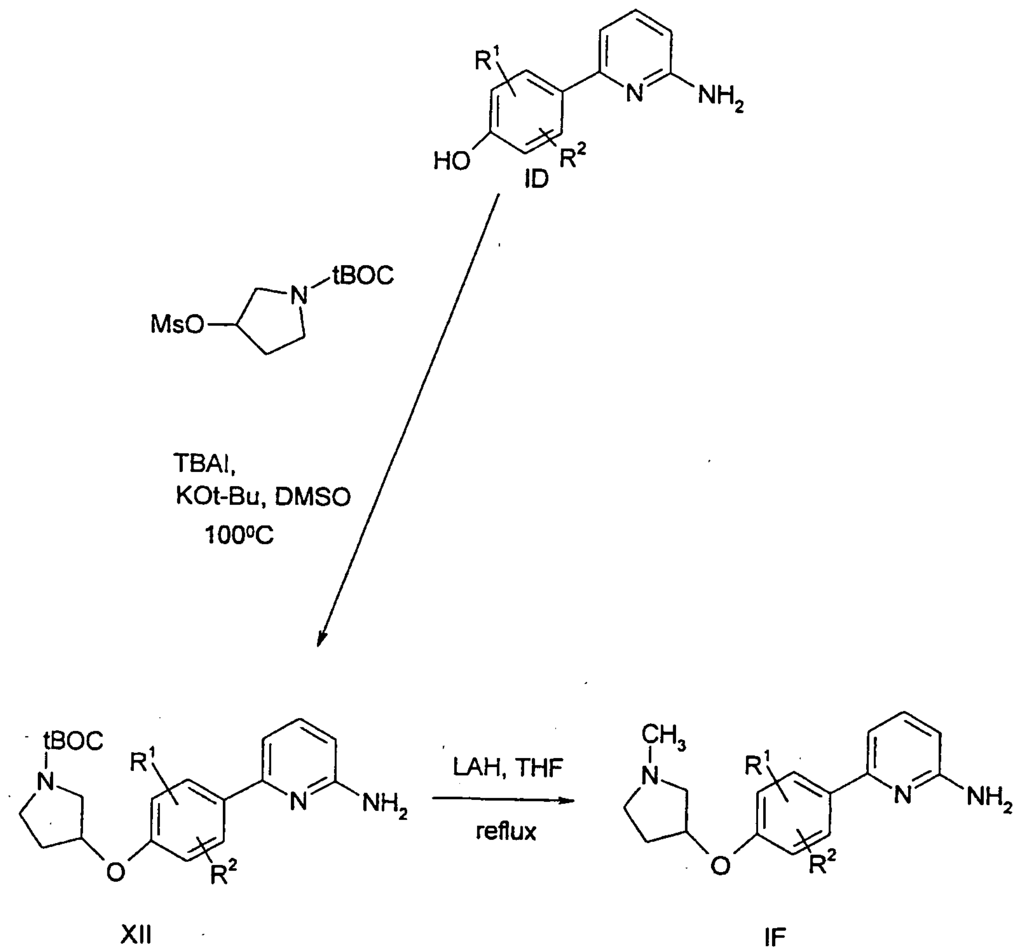
SCHEME 2


IA
GX
K2CO3
DMF or acetone
GX
K2CO3/heat
DMF or acetone
1. Li AlH4, AlCl3
THF
OR
2. BH3 / THF
IB
(G=CH2C(=O)NR3R4)
IC
(G=CH2CH2NR3R4)

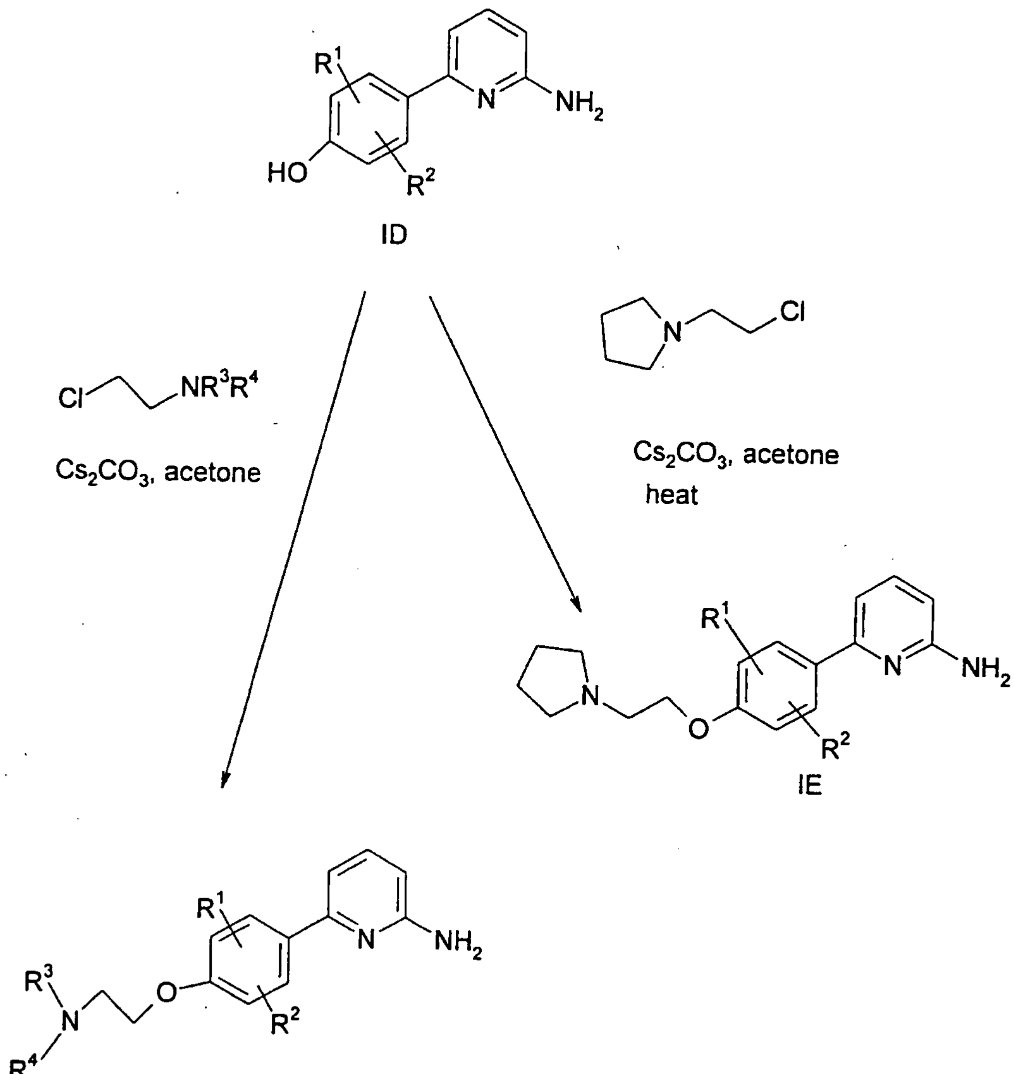
SCHEME 3


F
Br
BnO
X
(Bn = benzyl)
CH3
Br
BnO
CH3
XI
F
OH
B
OH
BnO
VIA
CH3
OH
B
OH
BnO
CH3
VIB
CONTINUE AS
WITH COMPOUND
VI IN SCHEME 1

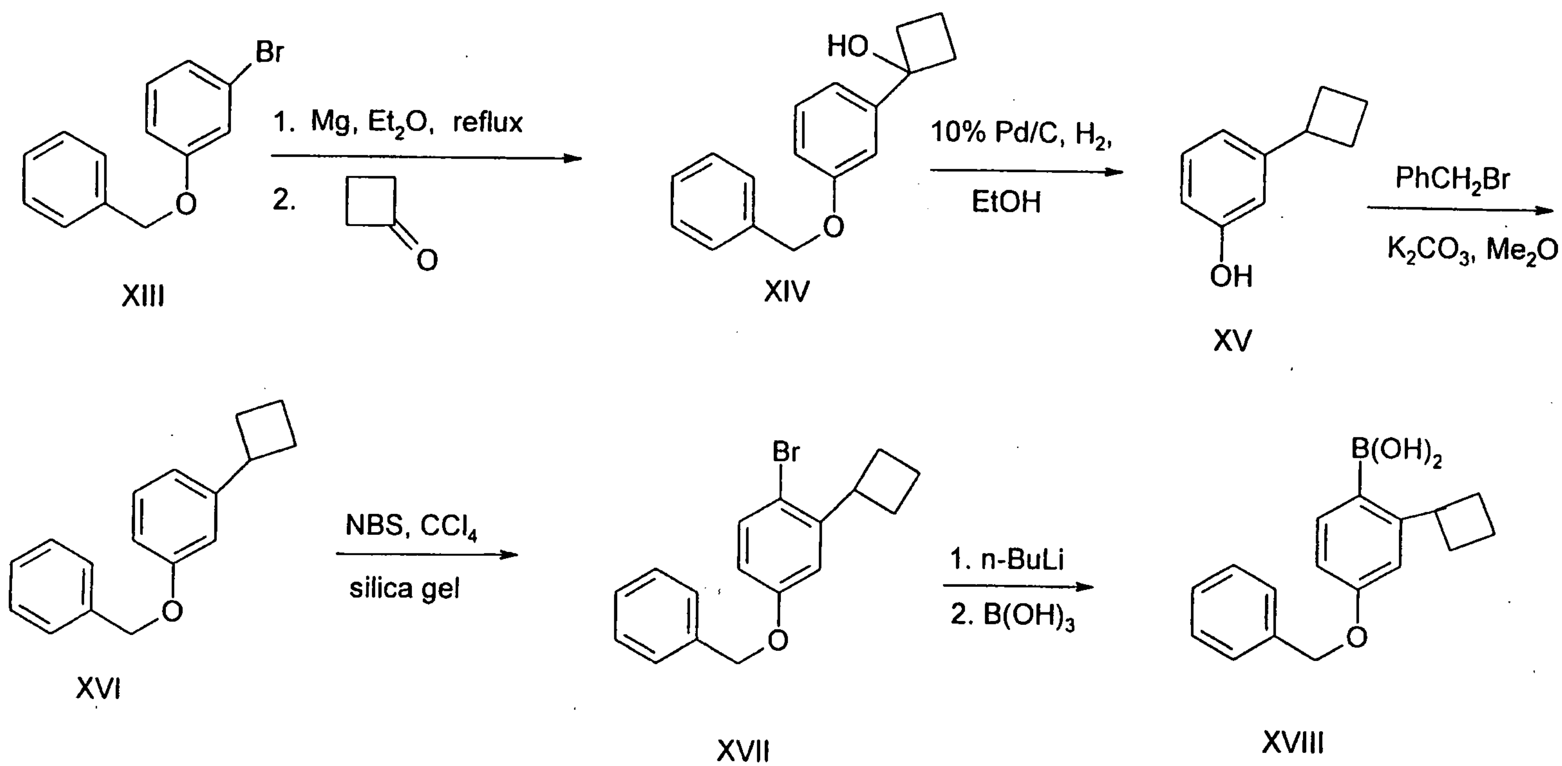
SCHEME 4


R1
R2
HO
N
NH2
ID
MsO
N
tBOC
TBAI,
KOt-Bu, DMSO
100°C
tBOC
N
O
XII
LAH, THF
reflux
CH3
IF

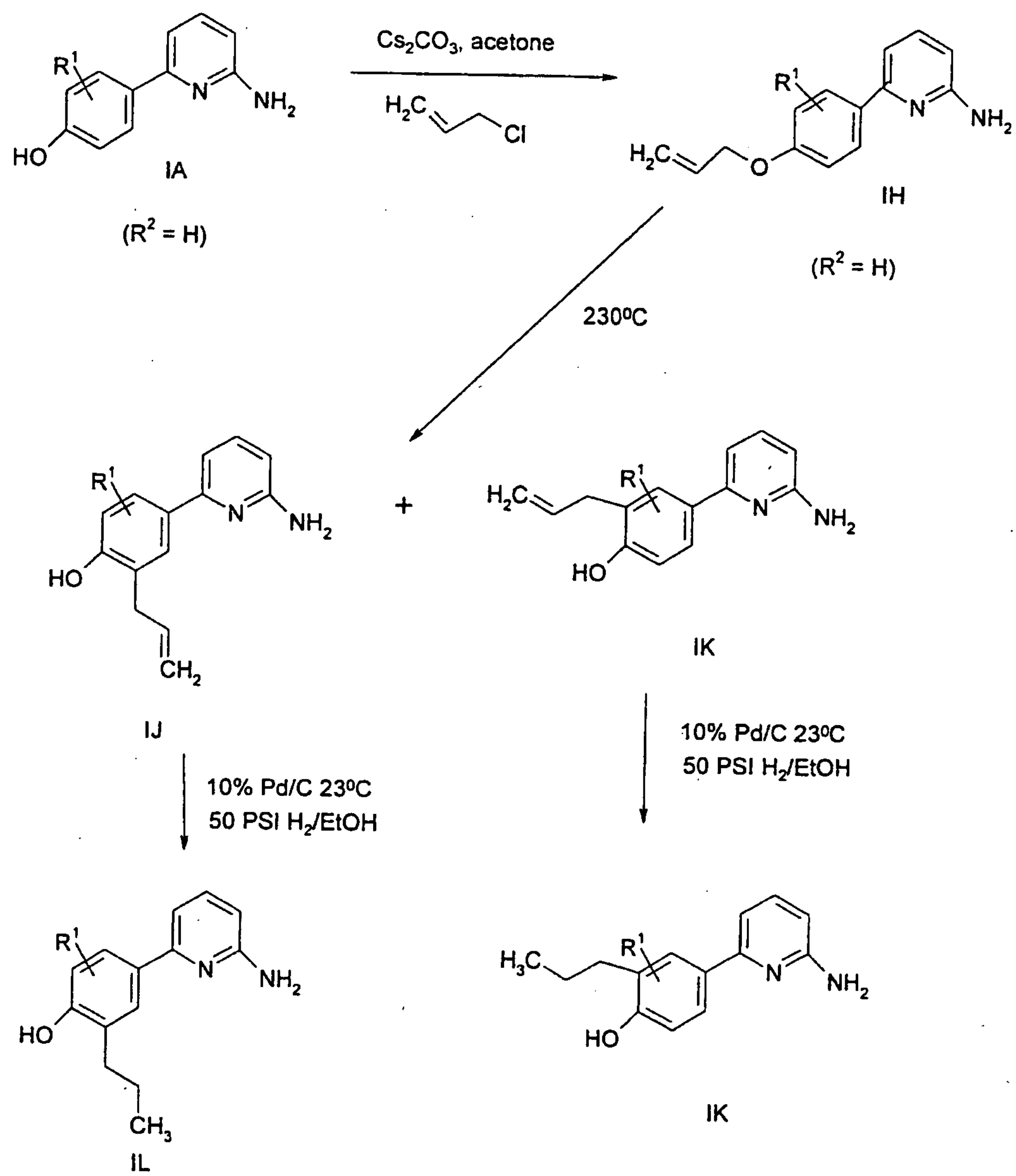
SCHEME 5


ID
IE
IG
Cs_2CO_3, acetone
Cs_2CO_3, acetone
heat
NR^3R^4
R^1
R^2
R^3
R^4
HO
NH_2

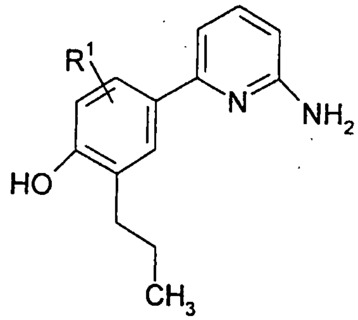
SCHEME 6


Br
1. Mg, Et_2O, reflux
2.
O
XIII
HO
XIV
10% Pd/C, H_2,
EtOH
OH
XV
$PhCH_2Br$
K_2CO_3, Me_2O
XVI
NBS, CCl_4
silica gel
Br
XVII
1. n-BuLi
2. $B(OH)_3$
$B(OH)_2$
XVIII

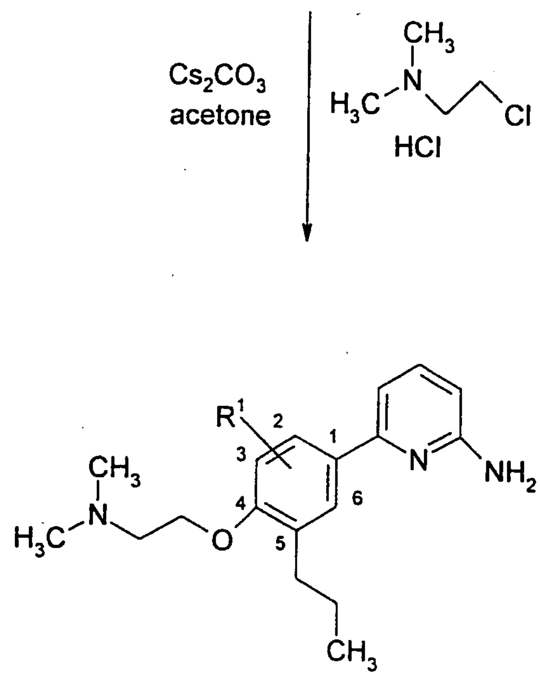
SCHEME 7


Cs2CO3, acetone
H2C Cl
R1
HO
NH2
N
IA
(R2 = H)
H2C O
IH
(R2 = H)
230°C
IJ
+
IK
CH2
10% Pd/C 23°C
50 PSI H2/EtOH
H3C
CH3
IL
IK

SCHEME 7 CONTINUED

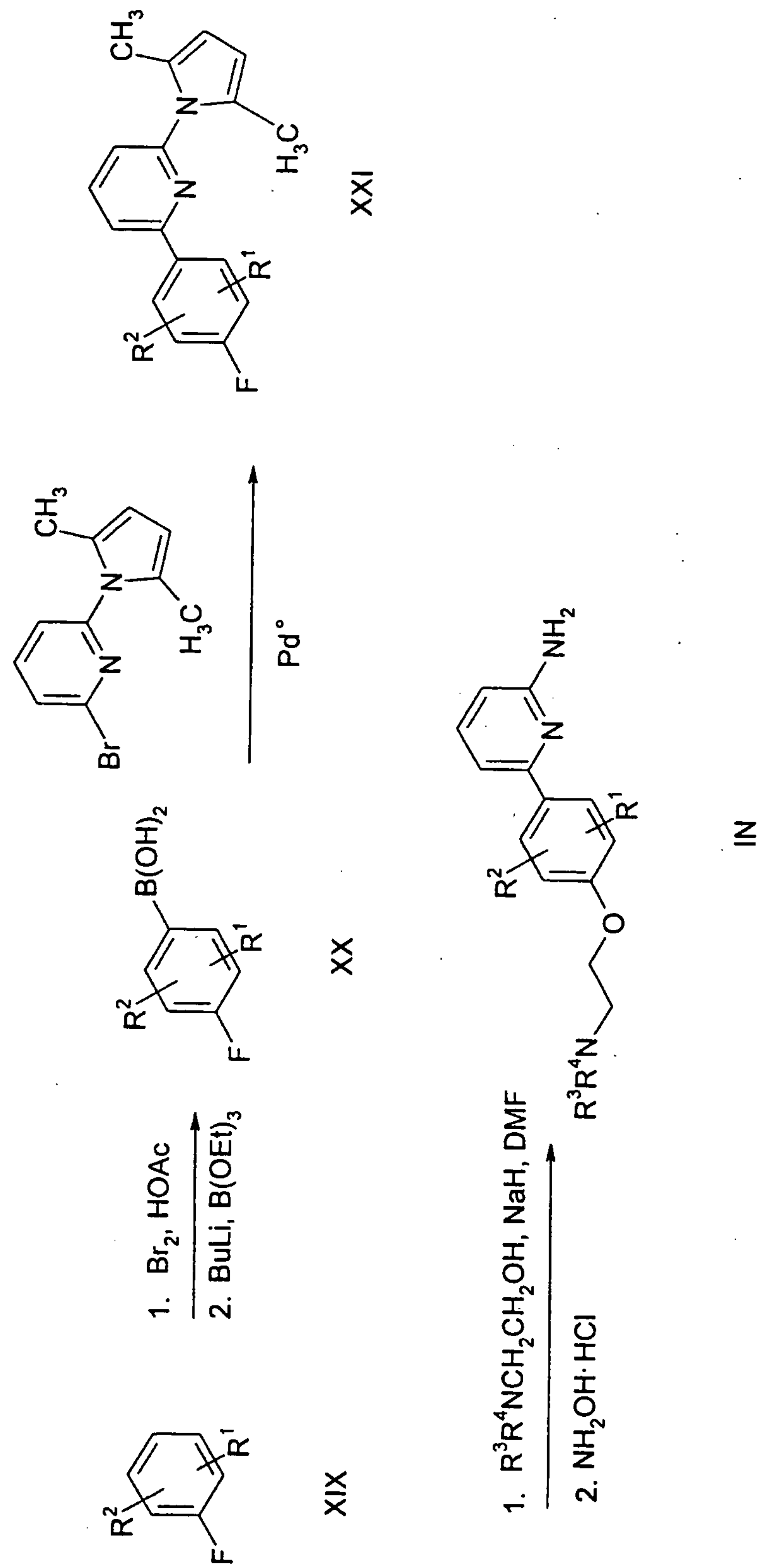


IL

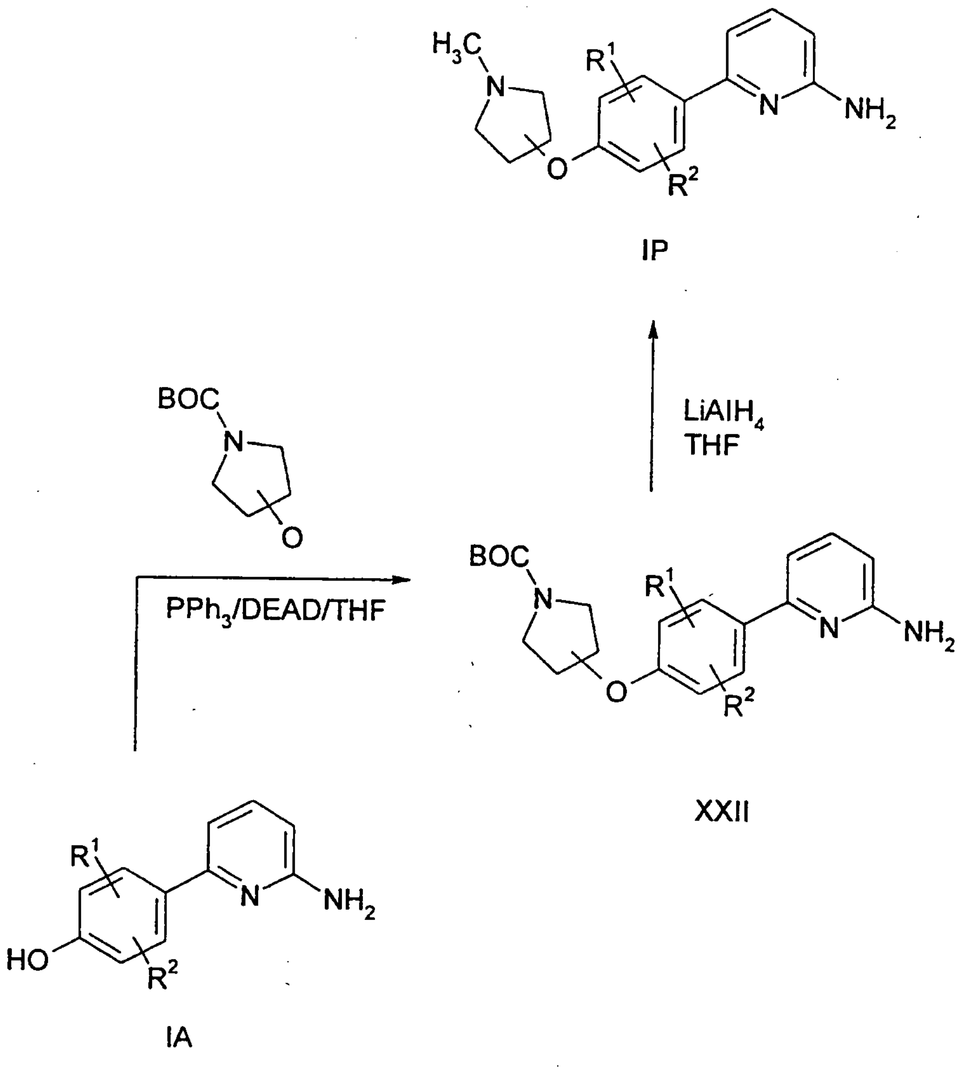


IM

SCHEME 8


XIX
1. Br_2, HOAc
2. BuLi, $B(OEt)_3$
XX
Pd°
XXI
1. $R^3R^4NCH_2CH_2OH$, NaH, DMF
2. $NH_2OH \cdot HCl$
IN

SCHEME 9

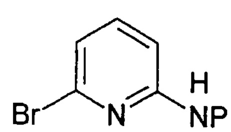

H3C
N
O
R1
R2
N
NH2
IP
LiAlH4
THF
BOC
N
O
PPh3/DEAD/THF
BOC
N
O
R1
R2
N
NH2
XXII
R1
HO
R2
N
NH2
IA

Scheme I illustrates a method for preparing compounds of the formula I wherein G is hydrogen, R^1 is -OR wherein R is (C_1-C_6)alkyl and R^2 is hydrogen. These compounds are referred to in Scheme I as compounds of the formula "IA".

Referring to Scheme 1, the compound of formula II is reacted with excess potassium carbonate and one equivalent of tosyl chloride in acetone, at a temperature from about 0°C to about 80°C, preferably at the reflux temperature of the reaction mixture. A compound of the formula RX, wherein R is (C_1-C_6)alkyl and X is iodo, chloro or bromo, is then added to the reaction mixture and the mixture is allowed to react at a temperature ranging from about 0°C to about 80°C, preferably at the reflux temperature of the mixture. This reaction yields a compound of the formula III. The compound of formula III is then converted into the corresponding compound of formula IV by reacting it with potassium hydroxide in ethanol, using water as the solvent. This reaction can be carried out at a temperature from about room temperature to about the reflux temperature of the reaction mixture. Preferably, the reaction mixture is heated to reflux and allowed to react at that temperature.

The compound of formula IV is then reacted with potassium carbonate and benzyl bromide in acetone, at a temperature from about room temperature to about 80°C, to form the corresponding compound of formula V. Preferably, the reaction is conducted at about the reflux temperature. Reaction of the resulting compound of formula V with butyl lithium in tetrahydrofuran (THF) at about -78°C, followed by the addition of triethyl borate and allowing the reaction mixture to warm to ambient temperature, yields the corresponding phenylboronic acid derivative of formula VI.

Reacting the phenylboronic acid derivative of formula VI with 2-bromo-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine (VII), sodium carbonate and tetrakis(triphenylphosphine)palladium(0) in ethanol/water or THF/water, at a temperature from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature, yields the corresponding compound of formula VIII. Alternatively, the reactant of formula VII can be replaced with another compound of the formula



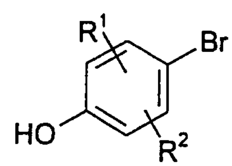
VIIA

wherein P is a nitrogen protecting group such as trityl, acetyl, benzyl, trimethylacetyl, t-butoxycarbonyl, benzyloxycarbonyl, trichloroethyloxycarbonyl or another appropriate nitrogen

protecting group and wherein the hydrogen that is bonded to the protected nitrogen is absent when P is a protecting group that forms a ring with the protected nitrogen, as in the case of P = 2,5-dimethylpyrrolyl. Such protecting groups are well known to those of skill in the art. The above compounds of the formula VIIA are either commercially available, known in the scientific literature or easily obtaining using well known methods and reagents.

The benzyl substituent can be removed from the compound of formula VIII by reacting such compound with ammonium formate in water or a lower alcohol solvent, or in a mixture of one or more of these solvents, at a temperature from about room temperature to about the reflux temperature of the reaction mixture. This reaction is preferably carried out at the reflux temperature in the presence of about 20% palladium hydroxide on carbon. The resulting compound of formula IX is then converted into the desired compound of formula IA by reacting it with hydroxylamine in a solvent selected from water, lower alcohols and mixtures of these solvents, at a temperature from about room temperature to about the reflux temperature of the solvent, preferably at about the reflux temperature.

The procedure of Scheme 1 can also be used to make compounds of the formula I wherein R^1 and R^2 are other than as specified above and depicted in the scheme. This can be accomplished by using a compound of the formula



IV'

as the starting material and then carrying out the series of reactions, as described above, that are represented in Scheme 1 as reactions IV→V→VI→VII→VIII→IX→IA.

Scheme 2 illustrates a method for preparing compounds of the formula I wherein G is hydrogen into the corresponding compounds of formula I wherein G is other than hydrogen.

Referring to Scheme 2, a compound of the formula IA can be converted into the corresponding compound of formula IC by reacting it with the compound of the formula GX, wherein X is iodo, chloro, or bromo, and G is $CH_2CH_2NR^3R^4$, and potassium carbonate in either dimethylformamide (DMF) or acetone at a temperature from about room temperature to about the reflux temperature of the mixture, preferably at about the reflux temperature. Compounds of the formulae IC can also be formed, as illustrated in Scheme 2, as by first preparing the corresponding compounds of formula IB and then converting them, if so desired, into the corresponding compounds of formula IC. Compounds of formula IB can be formed by reacting the corresponding compounds of formula IA with a compound of the formula GX, wherein X is

defined as above and G is $CH_2C(=O)NR^3R^4$, and potassium carbonate, in either DMF or acetone, at a temperature from about room temperature to about the reflux temperature of the reaction mixture. This reaction also is preferably carried out at about the reflux temperature.

The resulting compounds of formula of IB can be converted into the corresponding compounds of formula IC by reacting them with lithium aluminum hydride and aluminum chloride in a THF solvent, or with borane in THF. Other aluminum hydride reducing agents can also be used, such as diisobutyl aluminum hydride. Diborane can also be used. This reaction is generally carroid out at temperatures ranging from room temperature to about the reflux temperature of the reaction mixture, and is preferably carried out at the reflux temperature. Other appropriate sovlents include other organic ethers such as ethyl ether, dioxane and glyme, THF is preferred solvent.

Scheme 3 illustrates how certain compounds of the formula I having different substituents R^1 and R^2 than are depicted in the processes of Scheme 1 can be prepared. Such compounds are prepared by a process similar to that depicted in Scheme 1, with the exception that the processes of Scheme 1 involved in the synthesis of compound VI are replaced with those depicted in Scheme 3. Specifically, when R^2 is hydrogen and R^1 is fluoro at the ortho position, the compound of formula X is converted to the corresponding phenylboronic acid in a manner analogous to the conversion of compounds of the formula V into those of the formula VI in Scheme 1. The resulting phenylboronic acid derivative is referred to in Scheme 3 as compound VIA. Similarly, as shown in Scheme 3, compounds of the formula I wherein R^1 and R^2 are both methyl and are both at an ortho position relative to the pyridine ring, may be prepared by converting the compound of formula XI, as shown in Scheme 3, into the corresponding phenylboronic acid derivative designated as compound VIB, in a matter analogous to the conversion of compounds of formula V into those of the formula VI in Scheme 1. The compounds of formulas VIA and VIB can then be transformed into the desired corresponding compounds of the formula I using procedures analogous to those shown in Scheme 1.

Scheme 4 exemplifies methods of preparing compounds of the formula I wherein G is NR^3R^4 and NR^3R^4 forms an N-methylpyrrolin-2-yl ring. Compounds of the formula I wherein G is NR^3R^4 and NR^3R^4 forms other nitrogen containing rings can be prepared in an analogous fashion. Referring to Scheme 4, the compound of formula ID is allowed to react with 3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester to form the compound of formula XII. Other nitrogen protecting groups such as $-C(=O)OCH_2C_6H_5$ and COOR (wherein R is benzyl, phenyl, t-butyl or a similar group) can be used to protect the pyrrolidine nitrogen. Also, the mesylate leaving group can be replaced with another appropriate leaving group. Preferably,

a catalytic amount of tetrabutylammonium iodide (TBAI) is added to the reaction mixture. This alkylation reaction is typically carried out in the presence of an alkali metal alkoxide, preferable potassium tert-butoxide, in a high boiling polar organic solvent such as dimethylsulfoxide (DMSO) or DMF, preferably DMSO. The reaction temperature can range from about 50°C to about 100°C, and is preferably about 100°C.

Reduction of the compound of formula XII yields the compound of formula IF. This reduction is preferably accomplished using lithium alluminum hydride as the reducing agent and tetrahydrofuran (THF) or another organic ether (e.g., ethyl ether or glyme) as the solvent. Other aluminum hydride reducing agents can also be used, such as diisobutyl aluminum hydride. Diborane can also be used. The foregoing reaction is generally conducted at a temperature from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature.

As illustrated in Scheme 5, alkylation of the compound of formula ID with 1-(2-chloroethyl)-pyrrolidine yields the compound of formula IE. This reaction is generally conducted in the present of a base such as cesium carbonate, potassium carbonate, or sodium carbonate, preferably cesium carbonate, in a solvent such as acetone, DMSO or acetonitrile, preferably acetone, at a temperature from about room temperature to about the reflux temperature, preferably at about the reflux temperature.

Compounds of the formula I wherein NR^3R^4 do not form a ring can also be prepared by the method illustrated in Scheme 5 and described above for the formation of the compound of formula IE. Structural formula IG, depicted in Scheme 5, includes such compounds.

Scheme 6 illustrates a method of preparing the benzeneboronic acid intermediates use in the syntheses described in Schemes 1 and 3 above wherein the benzene ring of the benzeneboronic acid contains a cycloalkyl substituent. Such intermediates can be used in the processes of Schemes 1 and 3 to form compounds of the formula I wherein one or both of R^1 and R^2 are cycloalkyl groups. Referring to Scheme 6, the compound of formula XIII is allowed to reflux, in the presence of magnesium metal, in THF or ethyl ether for about 8 hours, after which cyclobutanone is added to the reaction mixture. This reaction yields the compound of formula XIV. Reduction of the compound of formula XIV using, for example, hydrogen gas and 10% palladium on carbon, in a lower alcohol solvent such as ethanol, at a temperature of about room temperature, yields the corresponding compound of formula XV.

Reaction of the compound of formula XV with benzylbromide in the presence of a base such as potassium, cesium or sodium carbonate, in a solvent such as acetone, dichlorothane, chloroform or methylene chloride, at a temperature from about room temperature to about the

reflux temperature of the reaction mixture, preferably at about the reflux temperature, yields the corresponding compound of formula XVI.

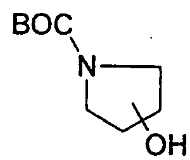
The compound of formula XVI that was formed in the above step is then brominated by reaction with N-bromosuccinamide (NBS) and silica gel in a chlorinated hydrocarbon solvent such as carbon tetrachloride, methylene chloride or chloroform. This reaction is typically carried out at room temperature. The compound of formula XVII that is produced in this reaction can then be converted into the benzeneboronic acid derivative of formula XVIII in the following manner. First, the compound of formula XVII, in a solvent such as THF, is cooled to a temperature of about -78°C to about -70°C, after which n-butyl lithium is added. After stirring the reaction mixture for about 1 hour, triethyl borate is added and the mixture is allowed to stir for an additional 1-3 hours. The benzeneboronic acid intermediate can then be isolated by methods well known to of those skilled in the art (e.g., quenching with ammonium chloride, adding water followed by concentrated hydrochloric acid, and then extracting with ethyl acetate).

Scheme 7 exemplifies a process for making compounds of the formula I wherein G is alkenyl, as well as compounds of the formula I wherein G is hydrogen and R^2 is an alkyl or alkenyl group. Referring to Scheme 7, the compound of formula IA is converted into the corresponding compound having the formula IH using an alkylation reaction analogous to that used to convert the compound of formula ID into that of formula IG in Scheme 5. Heating the resulting compound of formula IH to about 230°C yields the corresponding compounds of formulas IJ and IK. Hydrogenation of the compounds of formulas IJ and IK, using methods well know to those of skilled in the art (e.g., using hydrogen gas in ethanol of about 50 pounds per square inch, in the presence of 10% palladium on carbon at about room temperature) yields the corresponding alkyl derivatives of, respectively, formulas IL and IM. Alkylation of the compounds of formulas IL and IM (wherein G is hydrogen), using any of the alkylation methods described in Schemes 2, 4, and 5, and the appropriate alkylating agent, yields the corresponding desired compounds wherein G is other than hydrogen.

Scheme 8 illustrates an alternate method of preparing compounds of the formula I wherein G is $NR^3R^4(C_0\text{-}C_4)$ alkyl. Referring to Scheme 8, a compound of the formula XIX is reacted with bromine in acetic acid at a temperature from about 0°C to about 60°C, preferably at about room temperature. This reaction produces the corresponding compound having a bromine substituent para to the fluoro substituent, which can then be converted into the corresponding boronic acid derivative of formula XX as described above for the synthesis of compounds of the formula VI (in Scheme 1) and XVIII (in Scheme 6).

Addition of the 2,5-dimethylpyrroyl protecting group as described above for the synthesis of compounds of the formula VIII (in Scheme 1) yields the corresponding compound of formula XXI. The compound of formula XXI is then reacted with a compound of the formula R^3R^4NOH and an alkali metal hydride, preferably sodium hydride, in a polar, organic solvent such as DMF or DMSO, preferably DMF, at a temperature between about 50°C and about 110°C, preferably at about 100°C, to form a compound that is identical to the corresponding desired compound of formula IN, but for the presence of the 2,5-dimethylpyrrolyl protecting group. Removal of the protecting group, as described above for the preparation of compounds of the formula IA (in Scheme 1) yields the desired compound of formula IN.

Scheme 9 illustrates a method of synthesizing compounds of the formula I wherein G is an optionally substituted pyrrolidin-2-yl or pyrrolidin-3-yl group. Referring to Scheme 9, a compound of the formula IA is reacted with a compound of the formula



XXIII

triphenylphosphine and diethylazodicarboxylate or another water soluble azodicarboxylate in THF under standard Mistsunobo reaction conditions. Typically, the reactants are combined at about 0°C and then allowed to warm to room temperature. (If an alkyl substituent on the pyrrolidine nitrogen other than methyl is desired in the final product of formula IP, this can be accomplished by replacing the BOC group of formula XXIII with a group of the formula -C(=O)R, wherein R is the desired alkyl group).

The compound of formula XXII that is formed in the above reaction (or the corresponding -C(=O)R protected compound) can be converted into the desired product having formula IP (or a similar compound wherein the methyl substitutuent depicted in structure IP is replaced with another alkyl group) by reducing it. This reduction can be accomplished by reacting the product from the preceding reaction with lithium aluminum hydride and aluminum chloride in THF or borane in THF as described above for the formation of compounds of the formula IC.

The corresponding compound of formula I wherein the alkyl substituent on the pyrrolidine nitrogen formula IP is replaced with hydrogen can be obtained by reacting the compound of formula XXII with (or an alkyl analogue of XXII, as referred to above) with trifluoroacetic acid or hydrochloric acid in a solvent such as dioxane, or ether, preferably dioxane,

at a temperature from about 0°C to about reflux temperature of the reaction mixture, preferably at about the reflux temperature.

The starting materials used in the procedures of Schemes 1-9 are, the syntheses of which are not described above, either commercially available, known in the art or readily obtainable from known compounds using method that will be apparent to those skilled in the art.

The preparation of other compounds of the formula I not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

In each of the reactions discussed or illustrated above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, i.e., about 1 atmosphere, is preferred as a matter of convenience.

The compounds of formula I ("the active compounds of this invention") which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the active base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained.

The active compounds of this invention and their pharmaceutically acceptable salts are useful as NOS inhibitors i.e., they possess the ability to inhibit the NOS enzyme in mammals, and therefore they are able to function as therapeutic agents in the treatment of the aforementioned disorders and diseases in an afflicted mammal.

The active compounds of this invention and their pharmaceutically acceptable salts can be administered via either the oral, parental or topical routes. In general, these compounds are most desirably administered in dosages ranging from about 0.01 to about 250 mg per day, in single or divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.07 mg to about 21 mg per kg of body weight per day is most desirably employed. Variations may

nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the three routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of an active compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous

solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is also possible to administer the active compounds of the present invention typically when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, patches, ointments and the like, in accordance with standard pharmaceutical practice.

The ability of compounds of the formulae I to inhibit NOS may be determined using procedures described in the literature. The ability of compounds of the formulae I to inhibit endothelial NOS may be determined by using the procedures described by Schmidt et al. in Proc. Natl. Acad. Sci. U.S.A., 88, pp. 365-369 (1991) and by Pollock et al., in Proc. Natl. Acad. Sci. U.S.A., 88, pp. 10480-10484 (1991). The ability of compounds of the formulae I to inhibit inducible NOS may be determined using the procedures described by Schmidt et al., in Proc. Natl. Acad. Sci. U.S.A., 88 pp. 365-369 (1991) and by Garvey et al. in J. Biol. Chem., 269, pp. 26669-26676 (1994). The ability of the compounds of the formulae I to inhibit neuronal NOS may be determined using the procedure described by Bredt and Snyder in Proc. Natl. Acad. Sci. U.S.A., 87, 682-685 (1990).

The title compounds of Examples 1 and 2 below were tested according to the foregoing procedure and each exhibited an IC_{50} < 10 μM for inhibition of either inducible or neuronal NOS.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^1H NMR) and C^{13} nuclear magnetic resonance spectra were measured for solutions in deuterochloroform ($CDCl_3$) or in CD_3OD or CD_3SOCD_3 and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet, b, broad.

EXAMPLE 1

4-(6-AMINO-PYRIDIN-2-YL)-3-METHOXYPHENOL

A. Toluene-4-sulfonic acid, 4-bromo-3-methoxy-phenyl ester

Under a N_2 atmosphere in 300 mls of acetone was combined 7.00 grams (g) (37.04 mmol) of 4-bromoresorcinol and 32.76 g (237.0 mmol) of potassium carbonate followed by 6.246 g (37.04 mmol) of p-toluenesulfonyl chloride. The reaction was allowed to reflux with stirring for 16 hours at which point 5.96 mls (96.29 mmol) of methyl iodide was added. The solution was heated at 45°C for 48 hours. The reaction mixture was cooled, diluted with 300 mls of dietyl ether, filtered through a pad of Celite®, and concentrated in vacuo to yield 13.0 g of crude product as an orange oil which was chromatographed on 400g of silica gel 60 (EM Science) using 4:1 hexane: ethyl acetate to afford 10.10 g (76%) of the title compound.

^{1}H NMR ($CDCl_3$) δ 1.93 (s-6H), 2.30 (s-3H), 3.57 (s-3H), 6.88 (s-2H), 7.47 (d-1H), 7.62 (dd-1H), 8.17 (d-1H).

B. 4-Bromo-3-methoxyphenol

Under a nitrogen (N_2) atmosphere was dissolved 10.0 g (27.99 mmol) of the title compound from step A into a solution containing 300 mls of ethanol and 300 mls of water. To this solution was added 21.0 g (318 mmol) of potassium hydroxide and the resultant solution was heated to reflux for 2 hours. The reaction was cooled and concentrated in vacuo to approximately 150 mls and neutralized with acetic acid. This solution was extracted with ethyl ether (3 x 200 mls). The combined extracts were washed with saturated $NaCO_3$ (2 x 400 mls) followed by 3 percent potassium hydroxide (KOH) (4 x 100 mls). The aqueous layer was acidified with concentrated hydrochloric acid (HCl) and the aqueous layer was extracted with ethyl ether (3 x 200 mls). The organic extracts were washed with brine (1 x 200 mls), dried over magnesium sulfate filtered and concentrated in vacuo to afford 4.60 g (81%) of desired phenol which crystallized upon standing. Recrystallization from hexane/ethyl ether afforded 3.7 g of the title compound as a white crystalline product.

^{1}H NMR ($CDCl_3$) δ 1.92 (s-6H), 2.31 (s-3H), 6.89 (s-2H), 7.47 (d-1H), 7.63 (dd-1H), 8.18 (d-1H).

C. 4-Benzyloxy-1-bromo-2-methoxybenzene

Under a N_2 atmosphere in 50 mls of acetone was combined 3.689 g (18.17 mmol) of 4-bromo-3-methoxyphenol and 7.533 g (54.51 mmol) of potassium carbonate followed by 2.38 mls (19.99 mmol) of benzyl bromide. The reaction was followed to reflux with stirring for 16 hours and concentrated in vacuo. The solid residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (1 X 200 mls) and the

combined organic extracts were washed with 1M sodium hydroxide (NaOH) (2 X 100 mls) and brine (1 X 100 mls) and dried over sodium sulfate, filtered and concentrated in vacuo to yield 5.38 g (100%) of crude product as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 1.37 (s-9H), 1.93 (s-6H), 2.32 (s-3H), 6.08 (bs-1H), 6.96 (s-2H), 7.31 (m-2H), 7.89 (m-1H).

D. 4-Benzyloxy-2-methoxy-phenylboronic acid

Under a N_2 atmosphere in 75 mls of anhydrous THF was added 5.38 g (18.35 mmol) of 4-benzyloxy-1-bromo-2-methoxybenzene. The solution was cooled to -78°C and 8.07 mls (20.19 mmol) of a 2.5 M solution of butyl lithium was added dropwise and the temperature was maintained below -70°C. The reaction mixture was stirred at -78°C for 1.5 hours at which point 3.43 mls (20.19 mmol) of triethyl borate was added. The reaction was allowed to stir at -78°C for an additional 2.5 hours. The reaction mixture was quenched with 50 mls of saturated ammonium chloride (NH_4Cl) and allowed to warm to ambient temperature. Water (100 mls) was added to this solution, the pH was adjusted to 5.0 with 1 M HCl and the resultant solution was extracted with ethyl acetate (2 x 200 mls). The combined extracts were washed with brine (1 X 100 mls) and dried over sodium sulfate, filtered and concentrated in vacuo to yield crude product as a pink solid which was crystallized with ethyl acetate/hexane to afford 2.68 g (57%) of 4-benzyloxy-2-methoxy-phenylboronic acid as an off-white solid.^{1}H NMR ($CDCl_3$) δ 1.38 (s-9H), 1.93 (s-6H), 2.31 (s-3H), 4.10 (bs-2H), 5.57 (bs-1H), 6.50 (d-1H), 6.77 (d-1H), 6.92 (s-2H), 7.10 (dd-1H).

E. 2-(4-Benzyloxy-2-methoxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine.

Under a nitrogen atmosphere was combined 2.53 g (10.07 mmol) of 2-bromo-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine, 2.60g (10.07 mmol) of benzyloxy-2-methoxy-phenylboronic acid, 4.27 g (40.30 mmol) of sodium carbonate and 292 mg of tetrakis(triphenylphosphine)palladium(0) (0.25 mmol) in 27 mls of ethanol and 3 mls of water. The solution was allowed to reflux for 18 hours at which point the reaction mixture was concentrated in vacuo. The resultant yellow residue was partitioned between ethyl acetate (200 mls) and water (200 mls). The aqueous layer was extracted again with ethyl acetate (200 mls) and the combined organic extracts were washed with brine (1 X 200 mls) and dried over sodium sulfate, filtered and concentrated in vacum to yield crude product as a yellow oil which crystallized upon standing. Recrystallization of this solid from absolute ethanol afforded 3.10 g (80%) of the desired product as a tan solid.

^{1}H NMR ($CDCl_3$) δ 0.98 (t-6H), 1.33 (s-9H), 1.57 (m-4H), 1.98 (s-6H), 2.32 (s-3H), 3.30 (m-1H), 4.18 (bs-1H), 5.30 (bs-1H), 6.39 (d-1H, 6.68 (d-1H, 6.92 (s-2H), 7.20 (dd-1H).

^{13}C NMR ($CDCl_3$) 10.13, 20.25, 21.05, 26.61, 28.03, 55.29, 80.03, 110.77, 117.19, 127.69, 128.11, 120.80, 135.79, 136.09, 136.57, 144.30, 153.60

F. 4-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-2-yl]-3-methoxyphenol

Under a nitrogen atmosphere was combined 3.10 g (8.063 mmol) of 2-(4-benzyloxy-2-methoxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine and 15.25 g (241.9 mmol) of ammonium formate in 100 mls of methanol. The resultant slurry was allowed to reflux for 2 hours at which point the reaction mixture was allowed to cool to ambient temperature and passed through a 0.2 uM nylon membrane and the residue was washed with additional methanol. The organic solution was concentrated in vacuo and the resultant yellow residue was partitioned between ethyl acetate (200 mls) and water (200 mls). The aqueous layer was extracted again with ethyl acetate (200 mls) and the combined organic extracts were washed with brine (1 X 200 mls) and dried over sodium sulfate, filtered and concentrated in vacum to yield 2.011 g (85%) of the desired phenol as a tan solid.

^{1}H NMR ($CDCl_3$) δ 0.93 (t-6H), 1.60 (m-4H), 1.98 (s-6H), 2.30 (s-3H), 3.08 (m-3H), 3.22 (m-1H), 6.39 (d-1H), 6.61 (d-1H), 6.82 (dd-1H), 6.95 (s-2H)

G. 4-(6-Amino-pyridin-2-yl)-3-methoxyphenol

Under a nitrogen atmosphere was combined 5.92 g (20.11 mmol) of phenol and 16.77 g (241.3 mmol) of hydroxylamine hydrochloride in 120 mls of ethanol and 20 mls of water. The resultant mixture was allowed to reflux for 16 hours at which point the reaction mixture was allowed to cool to ambient temperature and concentrated in vacuo. The resultant yellow residue was partitioned between ethyl acetate (200 mls) and dilute sodium bicarbonate (200 mls). The aqueous layer was extracted again with ethyl acetate (2 X 200 mls) and the combined organic extracts were washed with brine (1 X 200 mls) and dried over sodium sulfate, filtered and concentrated in vacuum to yield crude product as a brown oil which was chromatographed on 300g of silica gel 60 (EM Science) using 4:1 hexane: ethyl acetate to afford 4.20 g (97%) of products a yellow foam which was crystallized from ethyl acetate/hexane to afford the title compound as a white solid.

^{1}H NMR ($CDCl_3$) δ 0.83 (t-6H), 1.33 (t-3H), 1.98 (s-6H), 2.00 (m-4H), 2.20 (m-2H), 2.32 (s-3H), 2.88 (q-2H), 4.08 (m-1H), 6.93 (m-3H), 7.18 (dd-1H), 7.42 (d-1H)

EXAMPLE 2

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

Under a nitrogen (N_2) atmosphere in 30 mls of acetone was combined 200 mg (0.92 mmol) of phenol and 383 mg (2.78 mmol) of potassium carbonate followed by 146 mg

(1.017 mmol) of N-(2-chloroethyl)dimethylamine hydrochloride. The reaction was allowed to reflux with stirring for 16 hours and concentrated in vacuo. The solid residue was partitioned between ethyl acetate and 1M sodium hydroxide (NaOH). The aqueous layer was extracted with ethyl acetate (1 X 200 mls) and the combined organic extracts were washed with 1M NaOH (2 x 100 mls) and brine (1 X 100 mls) and dried over sodium sulfate, filtered and concentrated in vacuo to yield crude product which was chromatographed on 75 g of silica gel 60 (EM Science) using 9:1:0.1 dichloromethane:methanol:ammominum hydroxide to afford 165 mg (62%) of the title compound as an off-white solid. Fifty milligrams of the corresponding hydrochloride salt of the title compound was prepared by dissolving a portion of the title compound in ethyl acetate and adding an ethyl acetate solution saturated with HCl.

EXAMPLE 3

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2,3-DIMETHYL-PHENYL]-PYRIDIN-2-YLAMINE

A. 3-Fluoro-6-bromo-o-xylene

To a 100 mL round-bottomed flask equipped with N_2 inlet were added 2.50 mL (20 mmol) 3-fluoro-o-xylene, 10 mL acetic acid, and 1.03 mL (20 mmol) bromine. After 12 hours at room temperature, the solution had turned colorless and was poured into water and extracted into petroleum ether. The organic layer was washed with water and 1 N sodium hydroxide solution, dried over sodium sulfate, and evaporated to a liquid, 4 g (100%), as a mixture of isomers.

^{1}H-NMR (δ, $CDCl_3$): 2.20, 2.25, 2.30, 2.38 (singlets, 6H), 6.78 (t, J=9, 6.8-7.4 (m, 1H).

^{13}C-NMR (δ, $CDCl_3$): 10.6, 10.7, 19.5, 19.6, 112.2, 112.5, 113.7, 113.9, 125.0, 126.1, 130.2, 138.2, 158.9, 160.0, 161.4, 162.4.

B. 3-Fluoro-o-xylene-6-boronic acid

To a 125 mL three-necked round-bottomed flask equipped with septum and N_2 inlet were added 4.08 g (20 mmol) 3-fluoro-6-bromo-o-xylene and 20 mL dry tetrahydrofuran. The solution cooled to -70°C, and 9.6 mL (24 mmol) of a 2.5 M solution of butyl lithium in hexane was added slowly over 5 minutes. The reaction was stirred 5 minutes at -70°C, then 4.08 mL (24 mmol) triethyl borate added, and stirring continued at -70°C for 5 minutes. The reaction was then allowed to warm to room temperature and stirred for 16 hours, then poured into dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was triturated with hexane to a white solid, 2.06 g (64%).

^{1}H-NMR (δ, $CDCl_3$): 2.22 (s, 3H), 2.30 (s, 3H), 6.7-7.3 (m, 2H).

^{13}C-NMR (δ, $CDCl_3$): 25.4, 26.3, 111.5, 111.7, 112.1, 112.3, 124.9, 126.0, 126.1, 130.8, 130.9, 159.9, 160.6, 162.3, 163.0, .

C. 2-(2,5-Dimethylpyrrolyl)-6-[4-fluoro-2,3-dimethyl-phenyl]-pyridine

To a 100 mL round-bottomed flask equipped with condenser and N_2 inlet were added 3.08 g (12.27 mmol) 6-bromo-2-(2,5-dimethylpyrrolyl)pyridine, 2.06 g (12.27 mmol) 3-fluoro-o-xylene-6-boronic acid, 5.20 g (49.1 mmol) sodium carbonate, 140 mg tetrakistriphenylphosphinepalladium, 36 mL ethanol, and 4 mL water. The reaction was refluxed 4 hours, cooled, and poured into water, then extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford 3.2 g (89%) of a solid.

^{1}H-NMR (δ, $CDCl_3$): 2.16 (s, 6H), 2.23 (s, 3H), 2.25 (s, 3H), 5.88 (s, 2H), 6.94 (m, 1H), 7.16 (m, 2H), 7.33 (d, J=8, 1H), 7.86 (t, J=8, 1H).

^{13}C-NMR (δ, $CDCl_3$): 11.30, 13.38, 17.31, 106.80, 107.57, 112.15, 112.39, 119.92, 122.96, 123.70, 126.05, 126.42, 128.34, 136.95, 138.10, 139.81, 151.48, 159.99, 162.32.

MS (%): 295 (parent+1, 100).

D. 2-(2,5-Dimethylpyrrolyl)-6-[4-(2-dimethylamino-ethoxy)-2,3-dimethyl-phenyl]-pyridine

To a 100 mL round-bottomed flask equipped with septum and N_2 inlet were added 0.121 mL (1.2 mmol) 2-dimethylaminoethanol, 4 mL dry dimethylformamide, and 115 mg (2.4 mol) sodium hydride (60% in oil). The reaction was heated for 30 minutes to ensure complete formation of the alkoxide, cooled, and 294 mg (1.0 mmol) 2-(2,5-dimethylpyrrolyl)-6-[4-fluoro-2,3-dimethyl-phenyl]-pyridine added. The reaction was heated at 100°C for 18 hours, cooled, and poured into water, then extracted into ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using methanol/methylene chloride as eluant to afford 260 mg (72%) of an oil.

^{1}H-NMR (δ, $CDCl_3$): 2.18 (s, 6H), 2.22 (s, 3H), 2.27 (s, 3H), 2.37 (s, 6H), 2.79 (t, J=6, 2H), 4.11 (t, J=6, 2H), 5.88 (s, 2H), 6.79 (d, J=8, 1H), 7.13 (d, J=8, 1H), 7.22 (d, J=8, 1H), 7.34 (d, J=8, 1H), 7.82 (t, J=8, 1H).

^{13}C-NMR (δ, $CDCl_3$): 12.19, 13.41, 17.61, 45.81, 46.10, 58.39, 66.92, 106.65, 108.81, 119.46,123.05, 125.98, 127.97, 128.57, 133.22, 135.68, 137.90, 151.34, 156.84, 160.71.

MS (%): 364 (parent+1, 100).

E. 6-[4-(2-Dimethylamino-ethoxy)-2,3-dimethyl-phenyl]-pyridin-2-ylamine

To a 100 mL round-bottomed flask equipped with condenser and N_2 inlet were added 260 mg (0.716 mmol) 2-(2,5-dimethylpyrrolyl)-6-[4-(2-dimethylamino-ethoxy)-2,3-dimethyl-phenyl]-pyridine, 500 mg hydroxylamine hydrochloride, 9 mL ethanol, and 1 mL water. The reaction was refluxed 40 hours, cooled, poured into dilute hydrochloric acid, washed with ethyl acetate, adjusted to pH 12 with 6 N sodium hydroxide solution, and extracted twice into methylene chloride. The organic layer was dried over sodium sulfate and evaporated, then converted to the hydrochloride salt using HCl in ether to afford a hygroscopic solid, 182 mg (71%).

^{1}H-NMR (δ, $CDCl_3$): 2.16 (s, 3H), 2.18 (s, 3H), 2.32 (s, 6H), 2.73 (d, J=7, 2H), 4.05 (t, J=7, 2H), 4.65 (bs, 2H), 6.33 (d, J=8, 1H), 6.59 (d, J=7, 1H), 6.71 (d, J=8, 1H), 7.10 (d, J=8, 1H), 7.37 (t, J=8, 1H).

^{13}C-NMR (δ, $CDCl_3$): 12.13, 17.25, 46.07, 58.39, 66.92, 106.08, 108.75, 114.40, 125.79, 127.24, 134.23, 135.53, 137.68, 156.39, 157.91, 159.19.

MS (%): 286 (parent+1, 100).

Anal. Calc'd. for $C_{17}H_{23}N_3O{\bullet}2HCl{\bullet}5/4H_2O$: C 53.62, H 7.28, N 11.03. Found: C 53.68, H 7.12, N 10.86.

EXAMPLE 4

6-[4-(2-PYRROLIDINYL-ETHOXY)-2,3-DIMETHYL-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 3, using 2-pyrrolidinyl-ethanol, in 57% yield, as a hygroscopic solid.

^{1}H-NMR (δ, $CDCl_3$): 1.76 (m, 4H), 2.16 (s, 3H), 2.17 (s, 3H), 2.61 (m, 4H), 2.89 (t, J=6, 2H), 4.09 (t, J=6, 2H), 4.62 (bs, 2H), 6.34 (d, J=8, 1H), 6.59 (d, J=7, 1H), 6.71 (d, J=8, 1H), 7.09 (d, J=8, 1H), 7.38 (t, J=8, 1H).

^{13}C-NMR (δ, $CDCl_3$): 12.13, 17.25, 23.52, 54.85, 55.07, 67.78, 106.05, 106.62, 108.73, 114.44, 125.73, 127.24, 134.14, 135.49, 137.68, 156.39, 157.85, 159.22.

MS (%): 312 (parent+1, 100).

Anal. Calc'd. for $C_{19}H_{25}N_3O{\bullet}2HCl{\bullet}2H_2O$: C 54.29, H 7.43, N 10.00. Found: C 54.48, H 7.60, N 9.64.

EXAMPLE 5

6-[4-(4-(N-METHYL)PIPERIDINYLOXY)-2,3-DIMETHYL-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 3, using 4-hydroxy-N-methylpiperidine, in 56% yield, mp 110-130°C as the hydrochloride salt.

^{1}H-NMR (δ, $CDCl_3$): 1.8-2.0 (m, 4H), 2.16 (s, 6H), 2.24 (s, 3H), 2.6 (m, 4H), 4.3 (m, 1H), 4.62 (bs, 2H), 6.33 (d, J=8, 1H), 6.58 (d, J=8, 1H), 6.71 (d, J=8, 1H), 7.06 (d, J=8, 1H), 7.37 (t, J=8, 1H).

^{13}C-NMR (δ, $CDCl_3$): 12.2, 17.2, 20.9, 30.7, 46.2, 52.4, 106.0, 110.9, 114.3, 127.0, 135.7, 137.6, 140.1, 154.7, 157.8, 159.1.

MS (%): 312 (parent+1, 100).

Anal. Calc'd. for $C_{19}H_{25}N_3O{\bullet}2HCl{\bullet}3/2H_2O$: C 55.48, H 7.35, N 10.21. Found: C 55.72, H 7.32, N 10.66.

EXAMPLE 6

6-[4-(2-DIMETHYLAMINO-ETHOXY)-3-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 2, using 2-methoxy-4-bromophenol, in 68% yield, mp 225-228°C as the hydrochloride salt.

^{1}H-NMR (δ, $CDCl_3$): 2.29 (s, 6H), 2.74 (t, J=6, 2H), 3.87 (s, 3H), 4.10 (t, J=6, 2H), 4.67 (bs, 2H), 6.32 (d, J=8, 1H), 6.88 (d, J=8, 1H), 6.95 (d, J=8, 1H), 7.38 (m, 2H), 7.51 (s, 1H).

^{13}C-NMR (δ, $CDCl_3$): 45.96, 55.86, 58.02, 67.15, 106.54, 110.15, 110.38, 113.04, 119.23, 132.99, 138.27, 148.83, 149.49, 155.66, 158.33.

MS (%): 288 (parent+1, 100).

Anal. Calc'd. for $C_{16}H_{21}N_3O_2{\bullet}2HCl{\bullet}H_2O{\bullet}½(C_4H_{10}O)$: C 52.05, H 7.28, N 10.12. Found: C 51.80, H 6.93, N 10.44.

EXAMPLE 7

6-[4-(2-PYRROLIDINYL-ETHOXY)-3-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 2, in 65.5% yield, mp 202-210°C as the hydrochloride salt.

^{1}H-NMR (δ, $CDCl_3$): 1.75 (m, 4H), 2.59 (m, 4H), 2.92 (t, J=6, 2H), 3.88 (s, 3H), 4.15 (t, J=6, 2H), 4.62 (bs, 2H), 6.33 (d, J=8, 1H), 6.89 (d, J=8, 1H), 6.97 (d, J=8, 1H), 7.39 (m, 2H), 7.52 (s, 1H).

^{13}C-NMR (δ, $CDCl_3$): 23.49, 54.69, 54.78, 55.91, 67.99, 106.50, 110.18, 110.38, 112.98, 119.26, 132.92, 138.27, 148.86, 149.46, 155.69, 158.27.

MS (%): 314 (parent+1, 100).

Anal. Calc'd. for $C_{18}H_{23}N_3O_2{\bullet}2HCl{\bullet}$ ½H_2O: C 54.69, H 6.63, N 10.63. Found: C 54.88, H 6.88, N 10.01.

EXAMPLE 8

6-{4-[2-(6,7-DIMETHOXY-3,4-DIHYDRO-1H-ISOQUINOLIN-2-YL)-ETHOXY]-3-METHOXY-PHENYL}-PYRIDIN-2-YLAMINE

Prepared as in Example 2, in 79% yield, mp 90-100°C as the hydrochloride salt.

^{1}H-NMR (δ, $CDCl_3$): 2.80 (m, 4H), 2.98 (t, J=6, 2H), 3.66 (s, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 4.23 (t, J=8, 2H), 4.66 (bs, 2H), 6.31 (d, J=8, 1H), 6.47 (s, 1H), 6.535 (s, 1H), 6.91 (d, J=8, 1H), 6.96 (d, J=8, 1H), 7.37 (m, 2H), 7.52 (s, 1H).

^{13}C-NMR (δ, $CDCl_3$): 28.50, 51.54, 55.84, 55.91, 56.04, 56.57, 67.30, 106.58, 109.42, 110.14, 110.41, 111.33, 113.07, 119.29, 125.95, 126.39, 133.04, 138.29, 147.15, 147.48, 148.80, 149.48, 155.60, 158.34.

MS (%): 436 (parent+1, 100).

Anal. Calc'd. for $C_{25}H_{29}N_3O_4$•2HCl•5/4H_2O: C 56.55, H 6.36, N 7.91. Found: C 56.59, H 6.19, N 7.70.

EXAMPLE 9

6-{3-METHOXY-4-[2-(4-PHENETHYL-PIPERAZIN-1-YL)-ETHOXY]-PHENYL}-PYRIDIN-2-YLAMINE

Prepared as in Example 2, in 78% yield, mp 167-182°C as the hydrochloride salt.

^{1}H-NMR (δ, $CDCl_3$): 2.4-2.6 (m, 10H), 2.75 (m, 2H), 2.825 (t, J=6, 2H), 3.86 (s, 3H), 4.13 (t, J=6, 2H), 4.70 (bs, 2H), 6.32 (d, J=8, 1H), 6.87 (d, J=8, 1H), 6.95 (d, J=8, 1H), 7.15 (m, 3H), 7.21 (m, 2H), 7.37 (m, 2H), 7.51 (s, 1H).

^{13}C-NMR (δ, $CDCl_3$): 32.56, 33.46, 52.98, 53.52, 55.82, 56.91, 60.37, 66.78, 106.47, 110.01, 110.39, 113.04, 119.21, 125.90, 128.25, 128.51, 128.58, 132.96, 138.18, 140.17, 148.73, 149.39, 155.52, 158.29.

MS (%): 433 (parent+1, 100).

Anal. Calc'd. for $C_{26}H_{32}N_4O_2$•3HCl•H_2O: C 55.77, H 6.66, N 10.01. Found: C 55.80, H 6.56, N 9.59.

EXAMPLE 10

6-{3-METHOXY-4-[2-(4-METHYL-PIPERAZIN-1-YL)-ETHOXY]-PHENYL}-PYRIDIN-2-YLAMINE

Prepared as in Example 2, in 71% yield, mp 75-95°C as the hydrochloride salt.

^{1}H-NMR (δ, $CDCl_3$): 2.19 (s, 3H), 2.4 (m, 4H), 2.6 (m, 4H), 2.78 (t, J=6, 2H), 3.83 (s, 3H), 4.10 (t, J=6, 2H), 4.66 (bs, 2H), 6.295 (d, J=8, 1H), 6.84 (d, J=8, 1H), 6.92 (d, J=8, 1H), 7.33 (m, 2H), 7.48 (s, 1H).

^{13}C-NMR (δ, $CDCl_3$): 45.97, 53.56, 54.98, 55.88, 56.92, 66.93, 106.51, 110.07, 110.43, 113.14, 119.23, 133.02, 138.23, 148.77, 149.46, 155.59, 158.31,.

MS (%): 343 (parent+1, 100).

Anal. Calc'd. for $C_{19}H_{26}N_4O_2$•3HCl•2H_2O•½($C_4H_{10}O$): C 48.05, H 7.30, N 10.67. Found: C 47.85, H 6.98, N 11.01.

EXAMPLE 11

6-{4-[2-(4-DIMETHYLAMINO-PIPERIDIN-1-YL)-ETHOXY]-3-METHOXY-PHENYL}-PYRIDIN-2-YLAMINE

Prepared as in Example 2, in 61% yield, mp 215-221°C as the hydrochloride salt.

^{1}H-NMR (δ, $CDCl_3$): 1.5 (m, 2H), 1.75 (m, 2H), 2.07 (m, 2H), 2.215 (s, 3H), 2.79 (t, J=6, 2H), 3.0 (m, 3H), 3.87 (s, 3H), 4.13 (t, J=6, 2H), 4.62 (bs, 2H), 6.33 (d, J=8, 1H), 6.88 (d, J=8, 1H), 6.96 (d, J=8, 1H), 7.38 (m, 2H), 7.50 (s, 1H).

^{13}C-NMR (δ, $CDCl_3$): 28.17, 30.28, 41.57, 53.69, 55.94, 56.90, 62.04, 67.07, 106.52, 110.18, 110.40, 113.05, 119.26, 132.96, 138.29, 148.80, 149.45, 155.66, 158.27.

MS (%): 371 (parent+1, 100).

Anal. Calc'd. for $C_{21}H_{30}N_4O_2$•3HCl•5/2H_2O: C 48.05, H 7.30, N 10.67. Found: C 48.34, H 7.28, N 10.66.

EXAMPLE 12

6-[4-(2-DIMETHYLAMINO-ETHOXY)-3-ETHOXY-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 2, (using 2-ethoxy-4-bromophenol), in 72% yield, mp 210-216°C as the hydrochloride salt.

^{1}H-NMR (δ, $CDCl_3$): 1.40 (t, J=7, 3H), 2.31 (s, 6H), 2.74 (t, J=6, 2H), 4.10 M, 4H), 4.64 (bs, 2H), 6.34 (d, J=8, 1H), 6.89 (d, J=8, 1H), 6.96 (d, J=8, 1H), 7.38 (m, 2H), 7.51 (s, 1H).

^{13}C-NMR (δ, $CDCl_3$): 14.88, 46.04, 58.06, 63.99, 64.43, 67.65, 106.50, 110.21, 112.10, 113.81, 119.38, 133.12, 138.27, 149.02, 149.22, 155.74, 158.28.

MS (%): 302 (parent+1, 100).

Anal. Calc'd. for $C_{17}H_{23}N_3O_2$•2HCl•½H_2O): C 53.27, H 7.84, N 10.96. Found: C 53.57, H 7.16, N 10.71.

EXAMPLE 13

6-[4-(2-PYRROLIDINYL-ETHOXY)-3-ETHOXY-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 2 (using 2-ethoxy-4-bromophenol), in 69% yield, mp 190-198°C as the hydrochloride salt.

^{1}H-NMR (δ, $CDCl_3$): 1.415 (t, J=7, 3H), 1.77 (m, 4H), 2.63 (m, 4H), 2.92 (t, J=6, 2H), 4.15 (m, 4H), 4.59 (bs, 2H), 6.35 (d, J=8, 1H), 6.91 (d, J=8, 1H), 6.97 (d, J=8, 1H), 7.41 (m, 2H), 7.51 (s, 1H).

^{13}C-NMR (δ, $CDCl_3$): 14.91, 23.49, 54.75, 54.79, 64.48, 68.36, 106.47, 110.27, 112.15, 113.65, 119.42, 132.99, 138.29, 148.94, 149.29, 155.80, 158.21.

MS (%): 328 (parent+1, 100).

Anal. Calc'd. for $C_{19}H_{25}N_3O_2$•2HCl•1½H_2O•½($C_4H_{10}O$): C 54.31, H 7.60, N 9.05. Found: C 54.41, H 7.37, N 9.41.

EXAMPLE 14

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2-ISOPROPYL-PHENYL]-PYRIDIN-2-YLAMINE

A. 1-Isopropyl-3-benzyloxy-benzene

Under a N_2 atmosphere in 300 mL of acetone was combined 20.0 ml (146.0 mmol) of 3-isopropylphenol and 40.35 g (291.9 mmol) of potassium carbonate followed by 17.36 mL (146.0 mmol) of benzyl bromide. The reaction was allowed to reflux with stirring for 16 hours. More (5 ml) benzyl bromide was added and heating was continued for another 24 hours. The reaction mixture was allowed to cool to ambient temperature and solids were removed by filtration and washed with acetone. The filtrate was concentrated *in vacuo* . The solid residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (1 X 300 mL) and the combined organic extracts were washed with 1M NaOH (1 X 200 mL) and brine (1 X 150 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* (100°C at 1 mm Hg) to yield 33.80 g (100%) of crude product (the title compound) as a yellow oil.

^{1}H NMR ($CDCl_3$) δ1.23 (d-6H; J = 7.06 Hz), 2.87 (m-1H), 5.05 (s-2H), 6.78-6.88 (m-2H), 7.21 (t-1H; J = 7.88 Hz), 7.30-7.45 (m-6H).

B. 1-Bromo-2-isopropyl-4-benzyloxy-benzene

Under a N_2 atmosphere in 400 mL of carbon tetrachloride was combined 33.50 g (148.0 mmol) of 1-isopropyl-3-benzyloxy-benzene, 27.66 g (155.4 mmol) of NBS (recrystallized from water), followed by 60.0 g of silica gel 60 (EM Science). The reaction was allowed to stir in the absence of light for 48 hours. Silica gel was then removed by filtration and was washed with dichloromethane. The combined filtrate was washed with 1M NaOH (2 X 200 mL) and brine (1 X 200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield 44.46 g (98 %) of crude product (the title compound) as a yellow liquid.

^{1}H NMR ($CDCl_3$) δ1.23 (d-6H; J = 6.84 Hz), 3.28-3.35 (m-1H), 5.02 (s-2H), 6.64 (dd-1H; J = 3.12 Hz; J = 8.72 Hz), 6.89 (d-1H; J = 2.91 Hz) 7.30-7.42 (m-6H).

C. 4-Benzyloxy-2-isopropyl-benzeneboronic acid

Under a N_2 atmosphere in 300 mL of anhydrous THF was added 44.46 g (145.7 mmol) of 1-bromo-2-isopropyl-4-benzyloxy-benzene. The solution was cooled to -78°C and

64.1 mL (160.2 mmol) of a 2.5 M solution of butyl lithium was added dropwise while maintaining the temperature below -70°C. The reaction mixture was stirred at -78°C for 1.0 hours at which point 27.26 mL (160.2 mmol) of triethyl borate was added. The reaction was allowed to stir at less than -60°C for an additional 2.0 hours. The reaction mixture was allowed to warm to ambient temperature and quenched with 200 mL of saturated NH_4Cl. Water (100 mL) was added to this solution, the pH was adjusted to 3.0 with conc HCl and the resultant solution was extracted with ethyl acetate (1 x 200 mL). The ethyl acetate extract was washed with brine (1 X 100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield crude product as a pink solid which was triturated with ethyl acetate/hexane to afford 16.80 g (43 %) of the title compound as a tan colored solid.

^{1}H NMR ($CDCl_3$) δ1.31 (d-6H; J = 6.85 Hz), 4.12-4.18 (m-1H), 5.13 (s-2H), 6.89 (dd-1H; J = 2.28 Hz; J = 8.50 Hz), 7.05 (d-1H; J = 2.28 Hz), 7.32-7.48 (m-5H), 8.15 (d-1H; J = 8.30 Hz).

D. <u>2-(4-Benzyloxy-2-isopropyl-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine</u>

Under a nitrogen atmosphere was combined 15.58 g (62.04 mmol) of 2-bromo-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine, 16.76 g (62.04 mmol) of 4-benzyloxy-2-isopropyl-benzeneboronic acid, 26.31 g (248.2 mmol) of sodium carbonate and 1.80 g of tetrakis(triphenylphosphine)palladium(0) (1.55 mmol) in 243 mL of ethanol and 27 mL of water. The solution was allowed to reflux for 72 hours at which point the reaction mixture was concentrated *in vacuo* . The resultant residue was partitioned between ethyl acetate (300 mL) and water (300 mL). The aqueous layer was extracted again with ethyl acetate (200 mL) and the combined organic extracts were washed with brine (1 X 200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield crude product as an amber solid which crystallized upon standing. Recrystallization of this solid from absolute ethanol:hexane afforded 21.35 g (87 %) of the title compound as a tan solid.

^{1}H NMR ($CDCl_3$) δ1.16 (d-6H; J = 6.85 Hz); 2.16 (s-6H), 3.28-3.31 (m-1H), 5.10 (s-2H), 5.88 (s-2H), 6.85 (dd-1H; J = 2.70; J = 8.51 Hz), 7.00 (d-1H; J = 2.49 Hz), 7.15 (d-1H; J = 7.89 Hz), 7.27 (d-1H; J = 8.51 Hz), 7.33 (dd-1H; J = 1.66 Hz; J = 7.06 Hz), 7.39 (dd-2H; J = 6.23 Hz; J = 7.68 Hz), 7.45 (d-2H; J = 7.27 Hz), 7.84 (dd-1H; J = 7.68 Hz; J = 7.89 Hz).

E. <u>4-[6-(2,5-Dimethyl-pyrrol-1-yl)-pyridin-2-yl]-3-isopropyl-phenol</u>

Under a nitrogen atmosphere was combined 21.20 g (53.46 mmol) of 2-(4-benzyloxy-2-isopropyl-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine and 67.42 g (1.06.9 mol) of ammonium formate and 2.00 g of palladium hydroxide in 300 mL of methanol. The resultant slurry was allowed to reflux. Over an eight hour period, 10.0 g of catalyst was added. The

reaction mixture was allowed to cool to ambient temperature and passed through a pad of celite to remove the catalyst. The celite pad was washed with methanol. The filtrate was concentrated *in vacuo* and the resultant yellow residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The aqueous layer was extracted again with ethyl acetate (200 mL) and the combined organic extracts were washed with brine (1 X 200 mL) and dried over sodium sulfate, filtered and concentrated *in vacuo* to yield 15.58 g (95 %) of desired phenol as a tan solid.

^{1}H NMR ($CDCl_3$) δ1.14 (d-6H; J = 6.85 Hz); 2.15 (s-6H), 3.21-3.24 (m-1H), 5.50 (bs-1H), 5.88 (s-2H), 6.61 (dd-1H; J = 2.49; J = 8.30 Hz), 6.80 (d-1H; J = 2.49 Hz), 7.14-7.17 (m-2H), 7.24 (d-1H; J = 0.83 Hz), 7.32 (d-1H; J = 7.68 Hz), 7.84 (dd-1H; J = 0.83 Hz; J = 8.51 Hz).

F. 4-(6-Amino-pyridin-2-yl)-3-isopropylphenol

Under a nitrogen atmosphere was combined 15.55 g (50.75 mmol) of phenol and 42.32 g (609.0 mmol) of hydroxylamine hydrochloride in 180 mL of ethanol and 30 mL of water. The resultant mixture was allowed to reflux for 16 hours at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo*. The resultant brown residue was partitioned between ethyl acetate (300 mL) and dilute sodium bicarbonate (300 mL). The aqueous layer was extracted again with ethyl acetate (4 X 100 mL) and the combined organic extracts were washed with brine (1 X 400 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield crude product as a brown gum. Chromatography on 300g of silica gel 60 (EM Science) starting with 3:2 hexane:ethyl acetate and increasing the ethyl acetate concentration yielded 10.0 g (86%) of aminopyridine as a pink solid which was recrystallized from ethyl acetate/hexane to afford the title compound as a tan solid.

^{1}H NMR (CD_3OD) δ1.11 (d-6H; J = 6.85 Hz); 3.03-3.10 (m-1H), 4.87 (bs-3H), 6.48-6.53 (m-2H), 6.60-6.63 (m-1H), 6.78 (d-1H; J = 2.28 Hz), 7.01 (d-1H; J = 8.30 Hz), 7.43-7.45 (m-1H).

G. 6-[4-(2-Dimethylamino-ethoxy)-2-isopropyl-phenyl]-pyridin-2-ylamine

Under a N_2 atmosphere in 175 mL of acetone was combined 3.0 g (13.14 mmol) of phenol and 17.13 g (52.56 mmol) of cesium carbonate followed by 2.83 g (19.71 mmol) of N-(2-chloroethyl)dimethylamine hydrochloride. The reaction was allowed to reflux with stirring for 16 hours and concentrated *in vacuo* . The solid residue was partitioned between ethyl acetate and water (H_2O). The aqueous layer was extracted with ethyl acetate (1 X 200 mL) and the combined organic extracts were washed with 1M NaOH (2 X 100 mL) and brine (1 X 100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield crude product

which was chromatographed on 80 g of silica gel 60 (EM Science) using 95:5:.05 dichloromethane:methanol:ammomium hydroxide to afford 3 g (76 %) of aminopyridine as a colorless oil. The corresponding hydrochloride salt of the title compound (2.95 g) was prepared by dissolving the title compound in dichloromethane (20 mL) and adding diethyl ether (3 mL) saturated with HCl. The mixture was stirred overnight and the white precipitant was filtered and dried.

^{1}H NMR (CD_3OD) δ1.19 (d-6H; J = 6.85 Hz), 2.99 (s-6H), 2.98-3.02 (m-1H), 3.61 (t-2H; J = 4.98 Hz), 4.41 (t-2H; J = 4.77 Hz), 6.68 (d-1H; J = 8.26 Hz), 6.81 (d-1H; J = 8.72 Hz), 6.97 (dd-1H; J = 8.51 Hz; J = 2.49 Hz), 7.09 (d-1H; J = 2.49 Hz), 7.26 (d-1H; J = 8.51 Hz), 7.74-7.78 (m-1H).

EXAMPLE 15

4-(6-AMINO-PYRIDIN-YL)-3-CYCLOPROPYL-PHENOL

A. 1-Cyclopropyl-3-benzyloxy-benzene

Cyclopropylmagnesium bromide (J.O.C., 57, 3499-3503, 1992) (formed in situ, 50 mmol in 35 ml of THF) was added via syringe to a stirred mixture of 1-bromo-3-benzyloxy-benzene (7.9 g, 30 mmol), [1,3-bis(diphenylphosphino)propane]nickel (II) dichloride (70 mg) and THF (35 ml).Upon completion of addition, the mixture was stirred at room temperature for 2 hours and then heated to reflux for 72 hours. The reaction mixture was cooled to room temperature and diluted with 100 ml of ethyl ether (Et_2O). The resultant mixture was washed with 5% hydrochloric acid (HCl), brine then dried with magnesium sulfate ($MgSO_4$) and concentrated in vacuo. The crude product was chromatographed on silica gel using hexanes: methylene chloride (5:1) to afford 4.0 g (36%) of the title compound.

^{1}H NMR ($CDCl_3$) δ: 0.67-0.70 (m, 2H), 0.93-0.96 (m, 2H), 1.87-1.90 (m, 1H), 5.04 (s, 2H), 6.69-6.71 (m, 2H), 6.77 (d, J=6 Hz, 1H), 7.17 (t, J=8 Hz, 1H), 7.32-7.45 (m, 5H).

B. 1-Bromo-2-cyclopropyl-4-benzyloxy-benzene

Prepared as in Example 14B using 1-cyclopropyl-3-benzyloxy-benzene, in 84% yield.

^{1}H NMR ($CDCl_3$) δ: 0.62-0.66 (m, 2H), 0.97-1.00 (m, 2H), 2.10-2.14 (m, 1H), 4.99 (s, 2H), 6.54 (d, J=3 Hz, 1H), 6.65 (d, J=4 Hz, 1H), 7.32-7.46 (m, 6H).

C. 2-Cyclopropyl-4-benzyloxy-benzeneboronic acid

Prepared as in Example ID using 1-bromo-2-cyclopropyl-4-benzyloxy-benzene, in 98% yield as a pink oil. The crude product was not purified but directly converted into 2-(2-cyclopropyl-4-benzyloxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine.

^{1}H NMR ($CDCl_3$) δ: 0.68-0.75 (m, 2H), 0.92-0.98 (m, 2H), 2.09-2.13 (m, 1H), 5.08 (s, 2H), 6.69-6.84 (m, 2H), 7.39-7.45 (m, 5H), 8.08 (d, J=8 Hz, 1H).

D. 2-(2-Cyclopropyl-4-benzyloxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine

Prepared as in Example 1E using 2-cyclopropyl-4-benzyloxy-benzeneboronic acid with 2-bromo-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine, in 50% yield.

^{1}H NMR ($CDCl_3$) δ: 0.65-0.67 (m, 2H), 0.82-0.86 (m, 2H), 2.04-2.11 (m, 1H), 2.17 (s, 6H), 5.07 (s, 2H), 5.88 (s, 2H), 6.62 (s, 1H), 6.84 (d, J=4 Hz, 1H), 7.14 (d, J=8 Hz, 1H), 7.32-7.44 (m, 6H), 7.54 (d, J=8 Hz, 1H), 7.83 (t, J=8 Hz, 1H).

MS (%): 395 (parent+1, 100).

E. 3-Cyclopropyl-4-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-2-yl]-phenol

Prepared as in Example 1F using 2-(2-cyclopropyl-4-benzyloxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine with ammonium formate and 20% $Pd(OH)_2$, in 97% yield.

^{1}H NMR ($CDCl_3$) δ: 0.60-0.62 (m, 2H), 0.79-0.81 (m, 2H), 1.98-2.00 (m, 1H), 2.11 (s, 6H), 5.83 (s, 2H), 6.42 (s, 1H), 6.65 (d, J=6 Hz, 1H), 7.09 (d, J=8 Hz, 1H), 7.24 (d, J=8 Hz, 1H), 7.51 (d, J=8 Hz, 1H), 7.80 (t, J=8 Hz, 1H).

F. 4-(6-Amino-pyridin-yl)-3-cyclopropyl-phenol

Prepared as in Example 1G using heating 3-cyclopropyl-4-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-2-yl]-phenol with NH_2OH•HCl in aqueous EtOH, in 67% yield.

^{1}H NMR ($CDCl_3$) δ: 0.47-0.51 (m, 2H), 0.73-0.77 (m, 2H), 1.90-1.94 (m, 1H), 6.16 (s, 1H), 6.31 (dd, J_1=8 Hz, J_2=2.5 Hz, 1H), 6.41 (d, J=8 Hz, 1H), 6.80 (d, J=8 Hz, 1H), 7.07 (d, J=8 Hz, 1H), 7.46 (t, J=8 Hz, 1H).

^{13}C NMR ($CDCl_3$) δ: 9.57, 13.18, 106.57, 111.21, 112.89, 115.14, 130.46, 138.19, 157.80.

MS (%): 227 (parent+1, 100).

EXAMPLE 16

6-[2-CYCLOPROPYL-4-(2-DIMETHYLAMINO-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 14G using of 4-(6-amino-pyridin-yl)-3-cyclopropyl-phenol and 2-dimethylaminoethyl chloride in a presence of Cs_2CO_3 in a boiling acetone (81% yield).

^{1}H NMR ($CDCl_3$, δ): 0.64-0.67 (m, 2H), 0.81-0.83 (m, 2H), 2.06-2.09 (m, 1H), 2.33 (s, 6H), 2.71 (t, J=6 Hz, 2H), 4.05 (t, J=6 Hz, 2H), 6.42 (d, J=8 Hz, 1H), 6.47 (s, 1H), 6.74 (d, J=8 Hz, 1H), 6.82 (d, J=8 Hz, 1H), 7.28 (d, J=8 Hz, 1H), 7.44 (t, J=8 Hz, 1H).

MS (%): 298 (parent+1, 100).

EXAMPLE 17

6-[2-CYCLOPROPYL-4-(2-PYRROLIDIN-1-YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 14G using of 4-(6-amino-pyridin-yl)-3-cyclopropyl-phenol and 1-(2-chloroethyl)-pyrrolidine in a presence of Cs_2CO_3 in a boiling acetone (84 % yield).

^{1}H NMR ($CDCl_3$, δ): 0.63-0.66 (m, 2H), 0.80-0.84 (m, 2H), 1.77-1.81 (m, 4H), 2.07-2.10 (m, 1H), 2.59-2.62 (m, 4H), 4.10 (bs, 2H), 6.44 (d, J=8 Hz, 1H), 6.48 (s, 1H), 6.74 (d, J=8 Hz, 1H), 6.82 (d, J=8 Hz, 1H), 7.29 (d, J=8 Hz, 1H), 7.45 (t, J=8 Hz, 1H).

MS (%): 324 (parent+1, 100).

EXAMPLE 18

3-[3-(6-AMINO-PYRIDIN-2YL)-4-CYCLOPROPYL-PHENOXY] -PYRROLIDINE-1-CARBOXYLIC ACID TERT-BUTYL ESTER

Prepared as in Example 29 using of 4-(6-amino-pyridin-yl)-3-cyclopropyl-phenol and 3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester in a presence of KOt-Bu in DMSO (69% yield).

^{1}H NMR ($CDCl_3$, δ): 0.63-0.67 (m, 2H), 0.82-0.86 (m, 2H), 1.44 (s, 9H), 2.02-2.15 (m, 3H), 3.45-3.60 (m, 4H), 4.49 (bs, 2H), 4.87 (bs, 1H), 6.42-6.44 (m, 2H), 6.67 (d, J=8 Hz, 1H), 6.82 (d, J=8 Hz, 1H), 7.28 (d, J=8 Hz, 1H), 7.45 (t, J=8 Hz, 1H).

MS (%): 396 (parent+1, 100).

EXAMPLE 19

6-[2-CYCLOPROPYL-4-(1-METHYL-PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

Prepared by a lithium aluminum hydride ($LiAlH_4$) reduction of 3-[3-(6-amino-pyridin-2yl)-4-cyclopropyl-phenoxy] -pyrrolidine-1-carboxylic acid tert-butyl ester, as described in Example 28, in 50% yield.

^{1}H NMR ($CDCl_3$) δ: 0.62-0.64 (m, 2H), 0.81-0.85 (m, 2H), 1.95-2.09 (m, 3H), 2.37 (s, 3H), 2.77-3.18 (m, 4H), 4.48 (bs, 2H), 4.81 (bs, 1H), 6.40-6.44 (m, 2H), 6.68 (d, J=8 Hz, 1H), 6.83 (d, J=8 Hz, 1H), 7.28 (d, J=8 Hz, 1H), 7.45 (t, J=8 Hz, 1H).

EXAMPLE 20

4-(6-AMINO-PYRIDIN-2-YL)-3-CYCLOBUTYL-PHENOL

A. 1-(3-Benzyloxy-phenyl)-cyclobutanol

In a flame-dried flask was placed magnesium and under a N_2 atmosphere added a solution of 1-bromo-3-benzyloxy-benzene (10.53 g, 40 mmol) in 30 ml of anhydrous ethyl ether. A resultant mixture was heated to reflux for 8 hours. The reaction mixture was then

cooled to 0°C followed by a dropwise addition of cyclobutanone (J.A.C.S., 90, 3404-3415,1968) (2.96 ml, 40 mmol) in 10 ml of anhydrous ethyl ether. The reaction was stirred at room temperature for 30 minutes and then cooled to 0°C and hydrolyzed with aqueous ammonium chloride (NH_4Cl) (20 ml). The organic extract was dried ($MgSO_4$) and concentrated in vacuo. The crude product was chromatographed on 300 g silica gel using hexanes-ethyl acetate 3:1 to afford 8.5 g (84%) of the title compound as a yellow oil.

^{1}H NMR ($CDCl_3$) δ: 1.60-1.66 (m, 1H), 2.03-2.11 (m, 1H), 2.33-2.36 (m, 2H), 2.50-2.54 (m, 2H), 5.07 (s, 2H), 6.88 (d, J=8 Hz, 1H), 7.09 (d, J=8 Hz, 1H), 7.13 (bs, 1H), 7.28-7.45 (m,3H).

B. 3-Cyclobutyl-phenol

Under a N_2 atmosphere in 50 ml of ethanol (EtOH) were combined 1-(3-benzyloxy-phenyl)-cyclobutanol (6g, 23.6 mmol) and 10% palladium on carbon (Pd/C) (1.5 g). A resultant mixture was hydrogenated (J.A.C.S., 90, 3404-3415,1968) at 40 psi for 24 hours. The reaction mixture was filtered through a pad of celite and concentrated under vacuo. The crude product was chromatographed on 120 g of silica gel using hexanes-ethyl acetate to afford 2.9 g (83%) of the title comound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.81-1.86 (m, 1H), 1.95-2.02 (m, 1H), 2.08-2.14 (m, 2H), 2.29-2.34 (m, 2H), 3.49 (q, J=8 Hz, 1H), 6.63 (d, J=6 Hz, 1H), 6.69 (bs, 1H), 6.77 (d, J=6 Hz, 1H), 7.15 (t, J=8 Hz, 1H).

C. 1-Cyclobutyl-3-benzyloxy-benzene

Prepared as in Example 1C using 3-cyclobutyl-phenol, in 98% yield.

^{1}H NMR ($CDCl_3$) δ: 1.81-1.86 (m, 1H), 1.98-2.02 (m, 1H), 2.11-2.15- (m, 2H), 2.30-2.34 (m, 2H), 3.52 (q, J=8 Hz, 2H), 5.05 (s, 2H), 6.78-6.86 (m, 3H), 7.21 (t, J=8 Hz, 1H), 7.32-7.45 (m, 5H).

D. 1-Bromo-2-cyclobutyl-4-benzyloxy-benzene

Prepared as in Example 14B using 1-cyclobutyl-3-benzyloxy-benzene, in 97% yield.

^{1}H NMR ($CDCl_3$) δ: 1.81-1.85 (m, 1H), 2.04-2.11 (m, 3H), 2.41-2.44 (m, 2H), 3.73 (q, J=8 Hz, 1H), 5.05 (s, 2H), 6.68 (d, J=8 Hz, 1H), 6.98 (bs, 1H), 7.35-7.46 (m, 6H).

^{13}C NMR ($CDCl_3$) δ: 17.84, 28.60, 40.64, 70.19, 113.09, 114.45, 114.85, 127.45, 127.99, 128.55, 133.02, 136.68, 145.51, 158.17.

E. 2-Cyclobutyl-4-benzyloxy-benzeneboronic acid

Prepared as in Example 1D using 1-bromo-2-cyclobutyl-4-benzyloxy-benzene, as a beige solid in 58% yield.

^{1}H NMR ($CDCl_3$) δ: 1.81-1.85 (m, 1H), 1.98-2.03 (m, 1H), 2.10-2.15 (m, 2H), 2.33-2.36 (m, 2H), 3.86 (q, J=8 Hz, 1H), 6.78 (d, J=8 Hz, 1H), 7.00 (bs, 1H), 7.38-7.74 (m, 6H).

F. 2-(2-Cyclobutyl-4-benzyloxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine

Prepared as in Example 1E using 2-cyclobutyl-4-benzyloxy-benzeneboronic acid and 2-bromo-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine, in 78% yield.

^{1}H NMR ($CDCl_3$) δ: 1.69-1.74 (m, 1H), 1.77-1.82 (m, 1H), 1.96-2.01 (m, 4), 2.16 (s, 6H), 3.91 (q, J=8 Hz, 1H), 5.11 (s, 2H), 5.87 (s, 2H), 6.84 (d, J=8 Hz, 1H), 7.02 (bs, 1H), 7.13 (d, J=8 Hz, 1H), 7.24-7.46 (m, 7H), 7.81 (t, J=8 Hz, 1H).

MS (%): 409 (parent+1, 100).

G. 3-Cyclobutyl-4-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-2-yl]-phenol

Prepared as in Example 1F using 2-(2-cyclobutyl-4-benzyloxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine, in 97% yield.

^{1}H NMR ($CDCl_3$) δ: 1.71-1.79 (m, 1H), 1.1.79-1.84 (m, 1H), 1.95-1.99 (m, 4H), 2.16 (s, 6H), 5.88 (s, 2H), 6.75 (d, J=8 Hz, 1H), 6.84 (bs, 1H), 7.13 (d, J=8 Hz, 1H), 7.21 (d, J=8 Hz, 1H), 7.30 (d, J=8 Hz, 1H), 7.82 (t, J=8 Hz, 1H).

MS (%): 319 (parent+1, 100).

H. 4-(6-Amino-pyridin-2-yl)-3-cyclobutyl-phenol

Prepared by heating 2-(2-cyclobutyl-4-benzyloxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine with NH_2OH•HCl in aqueous EtOH, as described in Example 1F, as a off-white solid, in 61 % yield.

^{1}H NMR ($CDCl_3$) δ: 1.62-1.66 (m, 1H), 1.72-1.78 (m, 1H), 1.92-1.97 (m, 4H), 3.65 (q, J=8 Hz, 1H), 6.37 (d, J=8 Hz, 1H), 6.54 (d, J=8 Hz, 1H), 6.58 (d, J=8 Hz, 1H), 6.79 (bs, 1H), 7.03 (d, J=8 Hz, 1H), 7.39 (t, J=8 Hz, 1H).

MS (%): 241 (parent+1, 100).

EXAMPLE 21

6-[2-CYCLOBUTYL-4-(2-DIMETHYLAMINO-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 14G using 4-(6-amino-pyridin-2-yl)-3-cyclobutyl-phenol and 2-dimethylaminoethyl chloride, as a pale yellow oil in 77% yield.

^{1}H NMR ($CDCl_3$) δ: 1.69-1.86 (m, 2H), 2.00-2.06 (m, 4H), 2.33 (bs, 6H), 2.73 (t, J=6 Hz, 2H), 3.80 (q, J=8 Hz, 1H), 4.10 (t, J=6 Hz, 2H), 4.43 (bs, 2H), 6.42 (d, J=8 Hz, 1H), 6.64 (d, J=8 Hz, 1H), 6.75 (d, J=8 Hz, 1H), 6.98 (bs, 1H), 7.21 (d, J=8 Hz, 1H), 7.43 (t, J=8 Hz, 1H).

^{13}C NMR ($CDCl_3$) δ: 17.91, 29.83, 38.26, 45.83, 58.27, 66.11, 105.95, 111.06, 113.43, 114.36, 130.23, 137.45.

MS (%): 312 (parent+1, 100).

EXAMPLE 22

6-[2-CYCLOBUTYL-4-(2-PYRROLIDIN-1-YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 14G using 4-(6-amino-pyridin-2-yl)-3-cyclobutyl-phenol and 1-(2-chloroethyl)-pyrrolidine in 69% yield.

^{1}H NMR ($CDCl_3$) δ: 1.69-1.86 (m, 5H), 1.99-2.06 (m, 4H), 2.61-2.64 (m, 4H), 2.91 (t, J=6 Hz, 2H), 3.80 (q, J=8 Hz, 1H), 4.14 (t, J=6 Hz, 2H), 4.43 (bs, 2H), 6.41 (d, J=8 Hz, 1H), 6.63 (d, J=8 Hz, 1H), 6.75 (d, J=8 Hz, 1H), 6.97 (bs, 1H), 7.20 (d, J=8 Hz, 1H), 7.43 (t, J=8 Hz, 1H).

^{13}C NMR ($CDCl_3$) δ: 17.91, 23.43, 38.27, 54.63, 55.04, 66.81, 106.26, 115.12, 113.34, 114,36, 130.24, 137.79.

MS (%): 338 (parent+1, 100).

EXAMPLE 23

6-[2-CYCLOBUTYL-4-(1-METHYL-PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

A. 3-[3-(6-Amino-pyridin-2-yl)-4-cyclobutyl-phenoxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

Prepared as in Example 29 using 4-(6-amino-pyridin-2-yl)-3-cyclobutyl-phenol and 3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester, (88% yield).

^{1}H NMR ($CDCl_3$) δ: 1.45 (s, 9H), 1.70-1.79 (m, 1H), 1.82-1.87 (m, 1H), 2.00-2.09 (m, 5H), 2.17-2.22 (m, 1H), 3.45-3.60 (m, 4H), 3.79 (q, J=9 Hz, 1H), 4.52 (bs, 2H), 4.92 (bs, 1H), 6.43 (d, J=8 Hz, 1H), 6.66 (d, J=8 Hz, 1H), 6.71 (d, J=8 Hz, 1H), 6.90 (bs, 1H), 7.20-7.24 (m, 1H), 7.44 (t, J=8 Hz, 1H).

B. 6-[2-Cyclobutyl-4-(1-methyl-pyrrolidin-3-yloxy)-phenyl]-pyridin-2-ylamine

Prepared by a $LiAlH_4$ reduction of 3-[3-(6-amino-pyridin-2-yl)-4-cyclobutyl-phenoxy]-pyrrolidine-1-carboxylic acid tert-butyl ester, as described in Example 28, in 73 % yield.

^{1}H NMR ($CDCl_3$) δ: 1.67-1.71 (m, 1H), 1.78-1.87 (m, 1H), 1.97-2.04 (m, 4H), 2.29-2.38 (m, 1H), 2.39 (s, 9H), 2.43-2.49 (m, 1H), 2.79-2.84 (m, 4H), 3.78 (q, J=9 Hz, 1H), 4.43 (bs, 2H), 4.84-4.88 (m, 1H), 6.42 (d, J=8 Hz, 1H), 6.64-6.68 (m, 2H), 6.90 (sb, 1H), 7.19 (d, J=8 Hz, 1H), 7.42 (t, J=8 Hz, 1H).

^{13}C NMR ($CDCl_3$) δ: 19.09, 29.93, 32.88, 38.12, 42.15, 55.16, 62.41, 76.81, 106.09, 111.68, 114.44, 130.29, 137.68, 145.41.

MS (%): 324 (parent+1, 100)

EXAMPLE 24

4-(6-AMINO-PYRIDIN-2-YL)-3-CYCLOPENTYL-PHENOL

A. 1-(3-Benzyloxy-phenyl)-cyclopentanol

To a flame-dried flask containing magnesium (Mg) was added a solution of 1-bromo-3-benzyloxy-benzene (10.53 g, 40 mmol) in 40 ml of anhydrous ethyl ether. Under a N_2 atmosphere the resultant mixture was heated to reflux for 8 hours. The reaction mixture was cooled to 0°C, followed by a dropwise addition of cyclopentanone (J.A.C.S., 90, 3404-3415, 1968) (3.54 ml, 40 mmol) in 10 ml of anhydrous ethyl ether. The reaction was stirred at room temperature for 30 minutes, then cooled to 0°C and hydrolyzed by aqueous ammonium chloride (NH_4Cl) (20 ml). The organic extract was dried ($MgSO_4$) and concentrated in vacuo. The crude product was chromatographed on 300 g silica gel using hexanes-ethyl acetate (EtOAc) 3:1 to afford 4g (37%) of the title compound as a pale yellow oil.

^1H NMR ($CDCl_3$) δ: 1.79-1.84 (m, 2H), 1.94-2.02 (m, 6H), 5.06 (s, 2H), 6.85 (d, J=8 Hz, 1H), 7.07 (d, J=8 Hz, 1H), 7.15 (bs, 1H), 7.23-7.44 (m, 6H).

B. 3-Cyclopentyl-phenol

Under a N_2 atmosphere in 30 ml of EtOAc were combined 1-(3-benzyloxy-phenyl)-cyclopentanol (2.8 g, 10.4 mmol), 3 drops of concentrated HCl, and 10% Pd/C (1 g). A resultant mixture was hydrogenated (Tetrahedran Assymetry, 1360, 1993) at 40 psi for 2 hours. The reaction mixture was filtered through a pad of celite and concentrated under vacuo to afford 1.3 g (77%) of the title compound as an oil.

^1H NMR ($CDCl_3$) δ: 1.56-1.79 (m, 6H), 1.99-2.04 (m, 1H), 2.93 (q, J=8 Hz, 1H), 6.62 (d, J=8 Hz, 1H), 6.71 (bs, 1H), 6.80 (d, J=8 Hz, 1H), 7.13 (d, J=8 Hz, 1H).

C. 1-Cyclopentyl-3-benzyloxy-benzene

Prepared by heating 3-cyclopentyl-phenol with benzyl bromide and potassium carbonate (K_2CO_3) in acetone, as described in Example 1C, to afford the title compound in 99% yield.

^1H NMR ($CDCl_3$) δ: 1.54-1.79 (m, 6H), 2.03-2.06 (m, 2H), 2.96 (q, J=8 Hz, 1H), 5.04 (s, 2H), 6.78 (d, J=8 Hz, 1H), 6.84-6.89 (m, 2H), 7.19 (t, J=8 Hz, 1H), 7.30-7.45 (m, 5H).

D. 1-Bromo-2-cyclopentyl-4-benzyloxy-benzene

Prepared by an NBS bromination of 1-cyclopentyl-3-benzyloxy-benzene, as described in Example 14B, in 76% yield.

^1H NMR ($CDCl_3$) δ: 1.49-1.53 (m, 2H), 1.66-1.80 (m, 4H), 2.03-2.09 (m, 2H), 3.34 (q, J=8 Hz, 1H), 5.01 (s, 2H), 6.65 (d, J=6 Hz, 1H), 6.90 (s, 1H), 7.31-7.41 (m, 6H).

E. 2-Cyclopentyl-4-benzyloxy-benzeneboronic acid

Prepared by lithiation of 1-bromo-2-cyclopentyl-4-benzyloxy-benzene with n-BuLi followed by addition of $B(OEt)_3$, as described in Example 1D, in 80% yield.

^1H NMR ($CDCl_3$) δ: 1.56-1.80 (m, 6H), 2.02-2.08 (m, 2H), 2.91-2.99 (m, 1H), 5.04 (s, 2H), 6.77 (d, J=8 Hz, 1H), 6.79-6.87 (m, 2H), 7.16-7.46 (m, 5H).

F. 2-(2-Cyclopentyl-4-benzyloxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine

Prepared by a Pd cross-coupling of 2-cyclopentyl-4-benzyloxy-benzeneboronic acid with 2-bromo-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine, as described in Example 1E, in 58 % yield.

^1H NMR ($CDCl_3$) δ: 1.55-1.60 (m, 4H), 1.74-1.78 (m, 2H), 1.91-1.95 (m, 2H), 2.17 (s, 6H), 3.30 (q, J=8 Hz, 1H), 5.10 (s, 2H), 5.89 (s, 2H), 6.86 (d, J=8 Hz, 1H), 7.03 (s, 1H), 7.16 (d, J=8 Hz, 1H), 7.25-7.47 (m, 7H), 7.84 (t, J=8 Hz, 1H).

MS (%): 423 (parent+1, 100).

G. 3-Cyclopentyl-4-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-2-yl]-phenol

Prepared by a reduction of 2-(2-cyclopentyl-4-benzyloxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-pyridine with ammonium formate and 20% palladium hydroxide on carbon ($Pd(OH)_2$ on C), as described in Example 1F, in 48% yield.

^1H NMR ($CDCl_3$) δ: 1.51-1.55 (m, 4H), 1.74-1.79 (m, 2H), 1.88-1.91 (m, 2H), 2.14 (s, 6H), 3.27 (q, J=8 Hz, 1H), 5.87 (s, 2H), 6.68 (d, J=8 Hz, 1H), 6.85 (bs, 1H), 7.15 (d, J=8 Hz, 1H), 7.23 (d, J=8 Hz, 1H), 7.33 (d, J=8 Hz, 1H), 7.83 (t, J=8 Hz, 1H).

MS (%): 333, (parent+1, 100).

H. 4-(6-Amino-pyridin-2-yl)-3-cyclopentyl-phenol

Prepared by heating 3-cyclopentyl-4-[6-(2,5-dimethyl-pyrrol-1-yl)-pyridin-2-yl]-phenol with $NH_2OH \cdot HCl$ in aqueous ethanol, as described in Example 1G, in 61% yield.

^1H NMR ($CDCl_3$) δ: 1.45-1.53 (m,4H), 1.61-1.70 (m, 2H), 1.86-1.93 (m, 2H), 3.08 (q, J=8 Hz, 1H), 4.64 (bs, 2H), 6.35 (d, J=8 Hz, 1H), 6.43 (d, J=8 Hz, 1H), 6.63 (d, J=8 Hz, 1H), 6.74 (bs, 1H), 7.02 (d, J=8 Hz,1H), 7.45 (t, J=8 Hz, 1H).

MS (%): 255 (parent+1, 100).

EXAMPLE 25

6-[2-CYCLOPENTYL-4-(2-DIMETHYLAMINO-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

Prepared by an alkylation of 4-(6-amino-pyridin-2-yl)-3-cyclopentyl-phenol with 2-dimethylaminoethyl chloride in a presence of Cs_2CO_3 in a boiling acetone, as described in Example 14G, (67% yield).

^{1}H NMR ($CDCl_3$) δ: 1.53-1.74 (m, 6H), 1.91-1.95 (m, 2H), 2.32 (s, 6H), 2.71 (t, J=6 Hz, 2H), 3.16 (q, J=8 Hz, 1H), 4.06 (t, J=6 Hz, 2H), 4.43 (bs, 2H), 6.42 (d, J=8 Hz, 1H), 6.66 (d, J=7 Hz, 1H), 6.74 (d, J=8 Hz, 1H), 6.92 (bs, 1H), 7.20 (d, J=8 Hz, 1H), 7.43 (t, J=8 Hz, 1H).

^{13}C NMR ($CDCl_3$) d 25.98, 35.42, 41.66, 45.92, 58.33. 65.82, 106.10, 110.86, 113.13, 114.61, 130.36, 137.61, 146.31, 157.92, 158.82.

MS (%): 326 (parent+1, 100).

EXAMPLE 26

6-[2-CYCLOPENTYL-4-(2-PYRROLIDIN-1YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

Prepared as in Example 14G using 4-(6-amino-pyridin-2-yl)-3-cyclopentyl-phenol and 1-(2-chloroethyl)-pyrrolidine in 43% yield.

^{1}H NMR ($CDCl_3$) δ: 1.53-1.95 (m, 12 H), 2.63 (bs, 4H), 2.90 (t, J=6 Hz, 2H), 3.18 (q, J=8 Hz, 1H), 4.12 (t, J=6 Hz, 2H), 4.45 (bs, 2H), 6.41 (d, J=8 Hz, 1H), 6.65 (d, J=7 Hz, 1H), 6.74 (d, J=7 Hz, 1H), 6.91 (bs, 1H), 7.19 (d, J=8 Hz, 1H), 7.42 (t, J=8 Hz, 1H).

^{13}C NMR ($CDCl_3$) δ: 23.47, 25.97, 35.43, 41.67, 54.70, 55.09, 66.84, 106.10, 111.05, 112.99, 114.62, 130.39, 137.61, 146.28, 157.87, 158.77.

MS (%): 352 (parent+1, 100).

EXAMPLE 27

3-[4-(6-AMINO-PYRIDIN-2YL)-3-METHOXY-PHENOXY]-PYRROLIDINE-1-CARBOXYLIC ACID TERT BUTYL ESTER

Under a N_2 atmosphere in 20 mL of anhydrous THF was combined 173 mg (0.92 mmol) of (R)-N-BOC-3-hydroxy-pyrrolidine, 200 mg (0.92 mmol) of 4-(6-amino-pyridin-2-yl)-3-methoxy-phenol and 267 mg (1.02 mmol) of triphenylphosphine. The reaction was allowed to cool to 0^0C and with stirring 160 ul of diethylazodicarboxylate (1.02 mmol) was added. The reaction mixture was allowed to warm to ambient temperature and the reaction was stirred for 18 hours at which point the reaction mixture was concentrated *in vacuo* and redissolved into ethyl acetate (150 mls) . The organic layer was washed with 1M NaOH (2 X 100 mL), with brine (1 X 100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield

crude product which was chromatographed on 40 g of silica gel 60 (EM Science) using 2:1 ethyl acetate:hexane to afford 397 mg of crude product (the title compound) which was carried directly into the next step.

EXAMPLE 28

6-[4-(1-METHYL-PYRROLIDIN-3-YLOXY)-2-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

Under a N_2 atmosphere in 15 mL of anhydrous THF was added 357 mg (0.92 mmol) of crude aminopyridine 3-[4-(6-amino-pyridin-2yl)-3-methoxy-phenoxy]-pyrrolidine-1-carboxylic acid tert butyl ester and 2.31 ml (2.31 mmol) of a 1.0 M solution of lithium aluminum hydride. The reaction mixture was heated to reflux for 2 hours and then cooled to ambient temperature. The reaction mixture was carefully quenched with 88 ul of water, 88 ul of 1N NaOH and 264 ul of water. The aluminum salts were filtered and washed with ethyl acetate and the filtrate was concentrated in vacuo to yield 290 mg of crude product as a greenish-yellow oil which was chromatographed on 25 g of silica gel 60 (EM Science) using 95:5:.05 dichloromethane:methanol:ammomium hydroxide to afford 85 mg (31 %) of the title compound as colorless oil, which was converted to 79 mg of HCl salt by dissolving in dichloromethane and adding 1 ml of an ether solution saturated with HCl and concentrating and triturating with ethyl acetate.

^{1}H NMR ($CDCl_3$) δ 1.98-2.03 (m-1H), 2.28-2.44 (m-2H), 2.38 (s-3H), 2.74-2.86 (m-3H), 3.78 (s-3H), 4.42 (bs-2H), 4.84-4.87 (m-1H), 6.37 (dd-1H; J = 0.83; J = 8.09), 6.45-6.51 (m-2H), 7.12 (dd-1H; J = 0.83; J = 7.68 Hz), 7.40-7.44 (m-1H), 7.63 (d-1H; J = 8.51 Hz).

EXAMPLE 29

4-[4-(6-AMINO-PYRIDIN-2YL)-3-METHOXY-PHENOXY]-PIPERIDINE-1-CARBOXYLIC ACID TERT BUTYL ESTER

Under a N_2 atmosphere in 15 mL of anhydrous DMSO was combined 57 mg (0.51 mmol) of potassium t-butoxide followed by 100 mg (0.46 mmol) of 4-(6-amino-pyridin-2-yl)-3-methoxy-phenol. N-BOC-4-hydroxy-piperidine mesylate (142 mg, 0.51 mmol) was then added and the resultant mixture was heated to 105°C for 4.5 hours. Another 142 mg (0.51 mmol) of mesylate was then added and the reaction was heated for an additional 75 minutes. The reaction was allowed to cool to ambient temperature and water (100 mls) was added.The aqueous solution was extracted with ethyl acetate (2X150 mls). The organic layer was washed with water (2X100 mls), 1M NaOH (2 X 100 mL), with brine (1 X 100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield crude product which was chromatographed

on 30 g of silica gel 60 (EM Science) using 2:1 ethyl acetate:hexane to afford 210 mg of crude product (the title compound) which was carried directly into the next step.

EXAMPLE 30

6-[2-METHOXY-4-(1-METHYL-PIPERIDIN-4-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

Lithium aluminum hydride reduction 4-[4-(6-amino-pyridin-2yl)-3-methoxy-phenoxy]-piperidine-1-carboxylic acid tert butyl ester as described above for the reduction of 3-[4-(6-amino-pyridin-2yl)-3-methoxy-phenoxy]-pyrrolidine-1-carboxylic acid tert butyl ester provided, after silica gel chromatography (95:5:0.05: CH_2Cl_2: MeOH: NH_4OH), 65 mg(45%-for two steps) of the title compound.

^1H NMR ($CDCl_3$) δ 1.81-2.03 (m-4H), 2.29 (s-3H), 2.26-2.30 (m-2H), 2.68 (m-2H), 3.79 (s-3H), 4.33-4.43 (m-3H), 6.37 (dd-1H; J = 0.62 Hz; J = 8.10 Hz), 6.51-6.57 (m-2H), 7.11 (dd-1H; J = 0.62 Hz; J = 7.68 Hz), 7.41 (t-1H; J = 7.68 Hz), 7.61 (d-1H; J = 8.52 Hz).

EXAMPLE 31

6-[4-(ALLYLOXY)-2-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

Under a N_2 atmosphere in 75 mL of acetone was combined 3.00 g (13.87 mmol) of 4-(6-amino-pyridin-2-yl)-3-methoxy-phenol and 9.04 g (27.75 mmol) of cesium carbonate followed by 3.39 mL (41.62 mmol) of allyl chloride. The reaction was allowed to heat at 45°C with stirring for 16 hours and concentrated *in vacuo* . The solid residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was washed with brine (1 X 100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield product as a yellow solid which was triturated with hexane anf filtered to afford 3.24 g (91 %) of crude product (the title compound) as a pale yellow solid.

^1H NMR ($CDCl_3$) δ 3.80 (s-3H), 4.45 (bs-2H), 4.55 (d-2H; J = 5.19 Hz), 5.28 (d-1H; J = 10.58 Hz), 5.41 (d-1H; J = 17.22 Hz), 6.05 (m-1H), 6.38 (d-1H; J = 8.09 Hz), 6.55 (m-2H), 7.11 (d-1H; J = 7.68 Hz),7.42 (t-1H; J = 7.67 Hz). , 7.64 (d-1H; J = 8.30 Hz).

EXAMPLE 32-33

4-(6-AMINO-PYRIDIN-2-YL)-3-METHOXY-6-ALLYL-PHENOL AND 4-(6-AMINO-PYRIDIN-2-YL)-3-METHOXY-2-ALLYL-PHENOL

Under a N_2 atmosphere in a round bottom flask equipped with a stir bar was added 4-(6-amino-pyridyl-2-yl)-3-methoxyphenol and allyl ether. The reaction vessel was evacuated under reduced pressure and was then purged with nitrogen gas. The reaction vessel was immersed in an oil bath heated to 230°C and was allowed to stir for 20 minutes at this temperature. Analysis after cooling by TLC(2:1 ethyl acetate: hexane) revealed some starting ether. The reaction vessel was

immersed in an oil bath heated to 230°C for an additional 20 minutes. The resultant brown oil was taken up in a methanol/ ethyl acetate solution and combined with 15 g of silica gel 60 (EM Science). This mixture was concentrated *in vacuo* and the resultant brown powder was placed on the head of a silica gel (150 g) column and chromatographed using 3:2 ethyl acetate: hexane to afford 1.4 g of crude 6-allyl phenol contaminated with some 2-allyl phenol. Crude 6-allyl phenol was rechromatographed using 1:1 ethyl acetate: hexane to afford 1.05 g (33 %) of 6-allyl phenol as a pale yellow solid.

^{1}H NMR ($CDCl_3$) δ 3.32 (d-2H; J = 6.22 Hz), 3.38 (s-3H), 4.68 (bs-2H), 5.03 (m-1H), 5.10 (m-1H), 5.95 (m-1H), 6.17 (s-1H), 6.37 (m-1H), 6.95 (m-1H), 7.28 (s-1H), 7.44 (m-1H).

^{1}H NMR ($CDCl_3$) 3.44 (s-3H), 3.46 (d-2H; J = 5.82 Hz), 4.59 (bs-2H), 5.03 (m-2H), 6.02 (m-1H), 6.38 (m-2H), 7.07 (d-1H; J = 7.68 Hz), 7.24 (m-1H), 7.42 (m-1H).

EXAMPLE 34

4-(6-AMINO-PYRIDIN-2-YL)-3-METHOXY-6-PROPYL-PHENOL

Under a N_2 atmosphere in a Parr bottle was dissolved 1.20 g (4.682 mmol) of 4-(6-amino-pyridin-2-yl)-3-methoxy-6-allyl-phenol in 25 mL of absolute ethanol. The ethanol solution was hydrogenated (50 PSI) for 45 minutes at ambient temperature. The reaction mixture was then filtered through a pad of celite which was washed with additional methanol. The combined filtrates were concentrated *in vacuo* to afford 1.20 g (99%) of the desired product.

^{1}H NMR (CD_3OD) δ 0.94 (t-3H; J = 7.47 Hz), 1.58 (m-2H), 2.52 (m-2H), 3.73 (s-3H), 6.42 (dd-1H; J =0.83 Hz; J = 8.30 Hz), 6.47 (s-1H), 6.88 (dd-1H; J = 0.83 Hz; J = 7.47 Hz), 7.19 (s-1H), 7.40 (dd-1H; J = 7.47 Hz; J = 8.09 Hz).

EXAMPLE 35

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2-METHOXY-5-PROPYL-PHENYL]-PYRIDIN-YLAMINE

Under a N_2 atmosphere in 20 mL of acetone was combined 150 mg (0.58 mmol) of 4-(6-amino-pyridin-2-yl)-3-methoxy-6-propyl-phenol and 819 mg (2.32 mmol) of cesium carbonate followed by 125 mg (0.87 mmol) of N-(2-chloroethyl)dimethylamine hydrochloride. The reaction was allowed to reflux with stirring for 16 hrs and concentrated *in vacuo* . The solid residue was partitioned between ethyl acetate (150 ml) and H_20. The organic extract was washed with brine (1 X 100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield crude product which was chromatographed on 25 g of silica gel 60 (EM Science) using 9:1 dichloromethane:methanol to afford 131 mg (69 %) of aminopyridine as a pale yellow solid. One hundred forty-five mg of the corresponding hydrochloride salt of the

title compound was prepared by dissolving the title compound in dichloromethane and adding diethyl ether saturated with HCl. The cloudy solution was concentrated *in vacuo*, isopropyl alcohol was added, and the solution was again concentrated *in vacuo* to provide a solid which was triturated with ethyl acetate.

^{1}H NMR ($CDCl_3$) δ 0.93 (t-3H; J = 7.47 Hz), 1.60 (m-2H), 2.40 (s-6H), 2.55 (m-2H), 2.74 (t-2H; J = 6.02 Hz), 3.82 (s-3H), 4.14 (t-2H; J = 6.02 Hz), 4.48 (bs-2H), 6.39 (d-1H; J = 8.09 Hz), 6.50 (s-1H), 7.14 (d-1H; J = 7.67 Hz), 7.43 (t-1H; J = 7.68 Hz), 7.51 (s-1H).

The title compounds of Example 36-42 were prepared using the procedures described in Example 27-30.

EXAMPLE 36

6-[2-ISOPROPYL-4-(PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.13 (d-6H; J = 6.86 Hz), 1.92-2.11 (m-2H), 2.43 (bs-2H), 2.84-3.22 (m-5H), 4.53 (bs-2H), 4.81-4.84 (m-1H), 6.38 (dd-1H; J = 0.62 Hz; J = 8.10 Hz), 6.60-6.69 (m-2H), 6.83 (d-1H; J = 2.49 Hz), 7.17 (d-1H; J= 8.52 Hz), 7.41 (t-1H; J = 7.47 Hz).

EXAMPLE 37

6-[2-ISOPROPYL-4-(PIPERIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.14 (d-6H; J = 6.85 Hz), 1.22-1.27 (m-1H), 1.40-1.55 (m-1H), 1.71-1.84 (m-2H), 1.97-2.02 (m-1H), 2.20 (bs-1H), 2.72-2.78 (m-3H), 3.15-3.22 (m-2H), 4.14-4.32 (m-2H), 4.47 (bs-2H), 6.42 (dd-1H; J = 0.83 Hz; J = 8.33 Hz), 6.65 (dd-1H; J = 0.83 Hz; J = 7.48 Hz), 6.75 (dd-1H; J = 2.71 Hz; J = 8.51 Hz), 6.89 (d-1H; J = 2.50 Hz), 7.18 (d-1H; J = 8.31 Hz), 7.44 (dd-1H; J = 7.48 Hz; J = 8.10 Hz).

EXAMPLE 38

6-[2-ISOPROPYL-4-(1-METHYL-AZETIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.12 (d-6H; J = 6.85 Hz), 2.40 (s-3H), 3.10 (m-2H), 3.16-3.22 (m-1H), 3.83 (m-2H), 4.47 (bs-2H), 4.73-4.79 (m-1H), 6.40 (d-1H; J = 8.09 Hz), 6.55 (dd-1H; J = 2.50 Hz; J = 8.30 Hz). 6.63 (d-1H; J = 7.47 Hz), 6.79 (d-1H; J = 2.70 Hz), 7.17 (d-1H; J = 8.30 Hz), 7.42 (t-1H; J = 7.68 Hz).

EXAMPLE 39

6-[2-ISOPROPYL-4-(1-METHYL-PIPERIDIN-4-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.15 (d-6H; J = 6.85 Hz), 1.82-1.90 (m-1H), 2.00-2.05 (m-1H), 2.31 (s-3H), 2.29-2.33 (m-2H), 2.70 (m-2H), 3.16-3.23 (m-1H), 4.34-4.45 (m-3H), 6.42 (dd-1H; J = 0.62 Hz; J = 8.10 Hz), 6.65 (dd-1H; J = 0.62 Hz; J = 7.47 Hz), 6.74 (dd-1H; J = 2.70 Hz; J =

8.51 Hz), 6.88 (d-1H; J = 2.70 Hz), 7.18 (d-1H; J = 8.52 Hz), 7.44 (dd-1H; J = 7.27 Hz; J = 8.10 Hz).

EXAMPLE 40

6-[2-ISOPROPYL-4-(1-METHYL-PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.12 (d-6H; J = 6.85 Hz), 1.98-2.02 (m-1H), 2.28-2.47 (m-2H), 2.38 (s-3H), 2.80-2.84 (m-3H), 3.15-3.20 (m-1H), 4.49 (bs-2H), 4.83-4.85 (m-1H), 6.38-6.41 (m-1H), 6.62-6.66 (m-2H), 6.85 (d-1H; J = 2.50 Hz), 7.17 (d-1H; J = 8.31 Hz), 7.39-7.43 (m-1H).

EXAMPLE 41

6-[2-ISOPROPYL-4-(1-METHYL-PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.11 (d-6H; J = 6.85 Hz), 1.94-2.02 (m-1H), 2.24-2.46 (m-2H), 2.37 (s-3H), 2.77-2.83 (m-3H), 3.14-3.21 (m-1H), 4.45 (bs-2H), 4.80-4.85 (m-1H), 6.38-6.40 (m-1H), 6.62-6.65 (m-2H), 6.84 (d-1H; J = 2.70 Hz), 7.14-7.17 (m-1H), 7.41 (dd-1H; J = 7.47 Hz; J = 8.02 Hz).

EXAMPLE 42

6-[2-ISOPROPYL-4-(2-METHYL-2-AZA-BICYCLO[2.2.1]HEPT-5-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.14 (d-6H), 1.48-1.96 (m-4H), 2.40 (s-3H), 2.44-2.88 (m-2H), 3.03 -3.06 (m-1H), 3.16-3.23 (m-2H), 4.43 (bs-2H), 4.64 (m-1H), 6.43 (dd-1H; J = 0.83 Hz; J = 8.30 Hz), 6.64-6.70 (m-2H), 6.86 (d-1H; J = 2.49 Hz), 7.17-7.20 (m-1H), 7.41-7.45 (dd-1H; J = 7.47 Hz; J = 8.09 Hz).

The title compounds of Examples 43-75 were prepared using procedures analogous to those described in Example 2.

EXAMPLE 43

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.34 (s-6H), 2.74 (t-2H), 3.79 (s-3H), 4.10 (t-2H), 4.49 (bs-2H), 6.38 (dd-1H; J = 8.09 Hz, 0.62 Hz), 6.54-6.58 (m-2H), 7.12 (dd-1H; J = 7.47 Hz, 0.83 Hz), 7.42 (t-1H; J = 7.68 Hz), 7.65 (m-1H).

EXAMPLE 44

6-{4-[2-(BENZYL-METHYL-AMINO)-ETHOXY]-2-METHOXY-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.34 (s-3H), 2.84 (t-2H; J = 6.01 Hz), 3.62 (s-2H), 3.79 (s-3H), 4.10 (t-2H; J = 6.01 Hz), 4.51 (bs-1H), 6.36 (d-2H; J = 8.09 Hz), 6.52-6.57 (m-2H), 7.12 (d-2H; J = 7.47 Hz), 7.22-7.36 (m-5H), 7.42 (t-1H; J = 7.89 Hz), 7.65 (d-1H; J = 8.30).

EXAMPLE 45

6-[2-METHOXY-4-(2-PYRROLIDIN-1-YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.78-1.82(m-4H), 2.60-2.65 (m-4H), 2.90 (t-2H; J = 5.82 Hz), 3.79 (s-3H), 4.13 (t-2H; J = 6.02 Hz), 4.44 (bs-2H), 6.37 (d-1H; J = 8.10), 6.55 (s-1H), 6.55-6.57 (m-1H), 7.11 (d-1H; J = 7.48 Hz), 7.39-7.43 (m-1H), 7.64 (d-1H; J = 7.89 Hz),.

EXAMPLE 46

2-(6-AMINO-PYRIDIN-2-YL)-5-(2-DIMETHYLAMINO-ETHOXY)-PHENOL

^{1}H NMR ($CDCl_3$) δ 2.34 (s-6H), 2.77 (t-2H), 4.09 (t-2H), 6.38-6.47 (m-2H), 7.06 (dd-1H; J = 2.49 Hz; J = 7.68 Hz), 7.46-7.51 (m-1H), 7.67-7.71 (m-1H).

EXAMPLE 47

2-[4-(6-AMINO-PYRIDIN-2-YL)-3-METHOXY-PHENOXY]-ACETAMIDE

^{1}H NMR (CD_3OD) δ 3.80 (s-3H), 4.53 (s-2H), 4.87 (bs-4H), 6.45 (d-1H; J = 8.09 Hz), 6.61 (dd-1H; J = 2.08 Hz; J = 8.51 Hz), 6.72 (d-1H; J = 1.87 Hz), 6.87 (d-1H; J = 7.47 Hz), 7.40-7.43 (m-2H).

EXAMPLE 48

6-[4-(2-AMINO-ETHOXY)-2-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR (CD_3OD) δ 3.08 (t-2H; J = 5.19 Hz), 3.78 (s-3H), 4.87 (bs-4H), 6.45 (dd-1H; J = 0.62 Hz; J = 8.30 Hz), 6.60 (dd-1H; J = 2.28 Hz; J = 8.30 Hz), 6.65 (d-1H; J = 2.28 Hz), 6.87 (dd-1H; J = 0.83; J = 7.47 Hz), 7.40-7.44 (m-2H).

EXAMPLE 49

6-{4-[2-(3,4-DIHYDRO-1H-ISOQUINOLIN-2-YL)-ETHOXY]-2-METHOXY-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.86-2.93 (m-4H), 2.98 (t-2H; J = 6.01), 3.77 (s-2H), 3.80 (s-3H), 4.22 (t-2H; J = 6.01 Hz), 6.36 (d-1H; J = 8.09 Hz), 6.57-6.61 (m-2H), 7.01-7.14 (m-5H), 7.42 (t-1H; J = 7.89 Hz), 7.68 (d-1H; J = 8.50).

EXAMPLE 50

2-[4-(6-AMINO-PYRIDIN-2-YL)-3-METHOXY-PHENOXY]-ETHANOL

^{1}H NMR ($CDCl_3$) δ 2.02 (bs-1H), 3.81 (s-3H), 3.81-3.84 (m-2H), 4.05-4.07 (m-2H), 4.55 (bs-1H), 6.40 (dd-1H; J = 0.62 Hz; J = 8.09 Hz), 6.53-6.58 (m-2H), 7.11-7.12 (m-1H), 7.44 (t-1H; J = 7.89 Hz), 7.64 (dd-1H; J = 2.49 Hz; J = 6.64 Hz).

EXAMPLE 51

6-{2-METHOXY-4-[2-(2,2,6,6-TETRAMETHYL-PIPERIDIN-1-YL)-ETHOXY]-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 0.86-1.65 (m-18 H), 2.73 (t-2H; J = 8.30), 3.33 (t-2H; J = 8.71 Hz), 3.82 (s-3H), 6.39 (d-1H; J = 8.30 Hz), 6.52-6.58 (m-2H), 7.13 (d-1H; J = 7.47 Hz), 7.43 (t-1H; J = 7.47 Hz), 7.65 (d-1H; J = 8.51 Hz).

EXAMPLE 52

6-{4-[2-(2,5-DIMETHYL-PYRROLIDIN-1-YL)-ETHOXY]-2-METHOXY-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.12 (d-6H; J = 6.23 Hz), 1.44-1.51 (m-2H), 2.07-2.15 (m-2H), 2.94-3.11 (m-2H), 3.27 (bs-2H), 3.80 (s-3H), 4.15-4.23 (m-2H), 4.52 (bs-2H), 6.38 (d-1H; J = 8.10 Hz), 6.53-6.58 (m-2H), 7.11 (d-1H; J = 7.47 Hz), 7.43 (t-1H; J = 7.26 Hz), 7.64 (d-1H; J = 8.51 Hz).

EXAMPLE 53

6-{4-[2-(2,5-DIMETHYL-PYRROLIDIN-1-YL)-ETHOXY]-2-METHOXY-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.19 (d-6H; J = 6.22 Hz), 1.41-1.44 (m-2H), 1.82-1.89 (m-2H), 2.76-2.78 (bs-2H), 3.02 (t-2H; J = 6.64 Hz), 3.80 (s-3H), 4.09 (t-2H; J = 6.64 Hz), 4.53 (bs-2H), 6.38 (d-1H; J = 8.09 Hz), 6.50-6.57 (m-2H), 7.11 (d-1H; J = 7.47 Hz), 7.43 (t-1H; J = 7.26 Hz), 7.64 (d-1H; J = 8.51 Hz).

EXAMPLE 54

2-[4-(6-AMINO-PYRIDIN-2-YL)-3-METHOXY-PHENOXY]-1-(2,2,6,6-TETRAMETHYL-PIPERIDIN-1-YL)-ETHANONE

LR/MS : M+H = 398 (theoretical = 398)

EXAMPLE 55

6-[2-METHOXY-4-(1-METHYL-PYRROLIDIN-2-YLMETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.23-2.35 (m-4H), 2.35 (s-3H), 2.65(m-1H), 2.90-2.99 (m-1H), 3.80 (s-3H), 4.46-4.50 (m-2H), 4.76 (bs-2H), 6.40 (dd-1H; J = 0.62 Hz; J = 8.10 Hz), 6.58-6.61 (m-2H), 7.08 (dd-1H; J = 0.81 Hz; J = 7.68 Hz). 7.41-7.46 (m-1H), 7.61 (dd-1H; J = 1.24; J = 8.10 Hz).

EXAMPLE 56

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2-PROPOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 0.97 (t-3H; J = 7.47), 1.71-1.80 (m-2H), 2.33 (s-6H), 2.72 (t-2H; J = 5.60 Hz), 3.90 (t-2H; J = 6.43 Hz), 4.07 (t-2H; J = 5.60 Hz), 4.45 (bs-2H), 6.36 (dd-1H; J = 0.41 Hz; J = 7.89 Hz), 6.54-6.57 (m-2H), 7.19 (d-1H; J = 7.68 Hz), 7.39 (t-1H; J = 7.47n Hz), 7.70 (d-1H; J = 8.10 Hz).

EXAMPLE 57

6-{4-[2-(BENZYL-METHYL-AMINO)-ETHOXY]-2-PROPOXY-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 0.99 (t-3H; J = 7.47), 1.74-1.82 (m-2H), 2.34 (s-3H), 2.84 (t-2H; J = 6.02 Hz), 3.62 (s-3H), 3.91 (t-2H; J = 6.52 Hz), 4.11 (t-2H; J = 5.81 Hz), 4.47 (bs-2H), 6.37 (d-1H; J = 7.89 Hz), 6.51-6.56 (m-2H), 7.21-7.44 (m-2H), 7.70 (d-1H; J = 8.10 Hz).

EXAMPLE 58

6-[4-(2-ETHOXY-ETHOXY)-2-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.23 (t-3H; J = 7.06 Hz), 3.55-3.61 (m-2H), 3.79 (s-3H), 3.76-3.79 (m-2H), 4.12-4.15 (m-2H), 4.49 (bs-1H), 6.37 (d-1H; J = 8.09 Hz), 6.54-6.56 (m-2H), 7.11 (d-1H; J = 7.47 Hz), 7.41 (dd-1H; J = 8.10 Hz; J = 1.46 Hz), 7.63 (dd-1H; J = 0.63 Hz; J = 7.87 Hz).

EXAMPLE 59

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2-ISOPROPOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.26 (d-6H; J = 6.02 Hz), 2.33 (s-6H), 2.72 (t-2H; J = 5.81 Hz), 4.07 (t-2H; J = 5.81 Hz), 4.41-4.47 (m-3H), 6.35 (d-1H; J = 8.09 Hz), 6.53-6.57 (m-2H), 7.20-7.23 (m-1H), 7.39 (t-1H; J = 7.68 Hz), 7.68 (d-1H; J = 8.50 Hz).

EXAMPLE 60

6-[4-(2-ETHOXY-ETHOXY)-2-ISOPROPOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.21-1.27 (m-9H), 3.58 (q-2H; J = 6.85 Hz), 3.75-3.78 (m-2H), 4.08-4.13 (m-1H), 4.39-4.47 (m-3H), 6.35 (d-1H; J = 8.09 Hz), 6.55-6.58 (m-2H), 7.22 (d-1H; J = 6.88 Hz), 7.37-7.41 (m-1H), 7.69 (d-1H; J = 7.88 Hz).

EXAMPLE 61

6-[2-METHOXY-4-(3-METHYL-BUTOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 0.96 (d-6H; J = 6.65 Hz), 1.68 (q-2H; J = 6.86 Hz), 1.80-1.87 (m-1H), 3.81 (s-3H), 4.01 (t-2H; J = 6.65 Hz), 4.42 (bs-2H), 6.37 (dd-1H; J = 0.83 Hz; J = 8.10

Hz), 6.51 (d-1H; J = 2.31 Hz), 6.55 (dd-1H; J = 2.28 Hz; J = 8.52 Hz), 7.13 (dd-1H; J = 0.64 Hz; J = 7.48 Hz), 7.42 (t-1H; J = 7.79 Hz), 7.65 (d-1H; J = 8.51 Hz).

EXAMPLE 62

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2-ETHOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.37 Hz (t-3H; J = 7.05 Hz), 2.34 (s-6H), 2.73 (t-2H; J = 5.60 Hz), 4.02 (q-2H; J = 7.05 Hz), 4.08 (t-2H; J = 5.60 Hz), 4.53 (bs-2H), 6.36-6.38 (m-1H), 6.55-6.58 (m-2H), 7.21 (d-1H; J = 7.68 Hz), 7.39-7.43 (m-1H), 7.71 (d-1H; J = 8.30 Hz).

EXAMPLE 63

6-{4-[2-(BENZYL-METHYL-AMINO)-ETHOXY]-2-ETHOXY-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.39 (t-3H; J = 7.06 Hz), 2.35 (s-3H), 2.84 (t-2H; J = 6.02 Hz), 3.62 (s-3H), 4.03 (q-2H; J = 6.84 Hz), 4.12 Hz (t-2H; J = 6.02 Hz), 4.43 (bs-2H), 6.38 (d-1H; J = 8.09 Hz), 6.51 (d-1H; J = 2.08 Hz), 6.55-6.57 (m-1H), 7.23-7.35 (m-5H), 7.42 (t-1H; J = 7.68 Hz), 7.73 (d-1H; J = 8.50 Hz).

EXAMPLE 64

6-[2-ETHOXY-4-(3-METHYL-BUTOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 0.97 (d-6H; J = 6.64 Hz), 1.39 (t-3H; J = 7.05 Hz), 1.60-1.75 (m-2H), 1.81-1.87 (m-1H), 3.99-4.06 (m-4H), 4.49 (bs-2H), 6.36 (d-1H; J = 7.89 Hz), 6.51 (d-1H; J = 2.08 Hz), 6.57 (dd-1H; J = 2.28 Hz; J = 8.50 Hz), 7.23 (d-1H; J = 7.47 Hz), 7.41 (t-1H; J = 7.68 Hz), 7.73 (d-1H; J = 8.50 Hz).

EXAMPLE 65

1-(6-AMINO-3-AZA-BICYCLO[3.1.0]HEX-3-YL)-2-[4-(6-AMINO-PYRIDIN-2-YL)-3-ETHOXY-PHENOXY]-ETHANONE

^{1}H NMR (CD) δ 1.38 (t-3H; J = 6.85 Hz), 2.00-2.20 (m-2H), 2.60-3.90 (m- 6H), 4.13-4.14 (m-2H), 4.77-4.87 (m-4H), 6.62-6.97 (m-4H), 7.44 (d-1H; J = 8.72 Hz), 7.90-7.95 (m-1H).

EXAMPLE 66

6-[2-ETHOXY-4-(2-PYRROLIDIN-1-YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.37 (t-3H; J = 7.05 Hz), 1.76-1.84 (m-4H), 2.57-2.63 (m-4H), 2.89 (t-2H; J = 5.81 Hz), 4.02 (q-2H; J = 5.85 Hz), 4.12 (t-2H; J = 5.81 Hz), 4.44 (bs-2H), 6.36 (d-1H; J = 8.09 Hz), 6.53-6.58 (m-2H), 7.22 (d-1H; J = 7.47 Hz), 7.40 (t-1H; J = 7.68 Hz), 7.71 (d-1H; J = 8.51 Hz).

EXAMPLE 67

3-{2-[4-(6-AMINO-PYRIDIN-2-YL)-3-ETHOXY-PHENOXY]-ETHYL}-3-AZA-BICYCLO[3.1.0]HEX-6-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.37-1.41 (m-5H), 1.78 (bs-2H), 2.47 (d-2H; J = 8.71 Hz), 2.55 (s-1H), 2.76-2.81 (m-2H), 3.05-3.08 (m-2H), 4.00-4.05 (m-4H), 4.47 (bs-2H), 6.35-6.38 (m-1H), 6.52-6.55 (m-2H), 7.20-7.25 (m-1H), 7.39-7.43 (m-1H), 7.69-7.72 (m-1H).

EXAMPLE 68

1-(6-AMINO-3-AZA-BICYCLO[3.1.0]HEX-3-YL)-2-[4-(6-AMINO-PYRIDIN-2-YL)-3-METHOXY-PHENOXY]-ETHANONE

^{1}H NMR (CD_3OD)-HCl salt δ 2.07-2.20 (m-2H), 2.47 (s-1H), 3.52-3.56 (m-1H), 3.64 (s-3H), 3.73-3.77 (m-1H), 3.88-3.93 (m-2H), 4.77-4.92 (m-2H), 6.71 (d-1H; J = 8.51 Hz), 6.81 (s-1H), 6.89 (d-1H; J = 8.92 Hz), 6.99 (d-1H; J = 7.47 Hz), 7.50 (d-1H; J = 8.71 Hz), 7.93 (d-1H; J = 7.47 Hz).

EXAMPLE 69

3-{2-[4-(6-AMINO-PYRIDIN-2-YL)-3-METHOXY-PHENOXY]-ETHYL}-3-AZA-BICYCLO[3.1.0]HEX-6-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.39 (s-2H), 2.50 (d-2H; J = 8.50 Hz), 2.57 (s-1H), 2.82 (t-2H; J = 6.01 Hz), 3.10 (d-2H; J = 8.90 Hz), 3.81 (s-3H), 4.04 (t-2H; J = 5.61 Hz), 4.45 (bs-1H), 6.39 (d-1H; J = 8,09 Hz), 6.51-6.56 (d-2H), 7.11(d-1H; J = 7.47 Hz), 7.43 (t-1H; J = 7.68 Hz), 7.63 (d-1H; J = 8.30 Hz).

EXAMPLE 70

6-[2-ISOPROPOXY-4-(2-PYRROLIDIN-1-YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.26 (d-6H; J = 6.02 Hz), 1.77-1.84 (m-4H), 2.61-2.65 (m-4H), 2.90 (t-2H; J = 5.81 Hz), 4.41-4.48 (m-3H), 6.35 (d-1H; J = 8.09 Hz), 6.53-6.58 (m-2H), 7.21 (d-1H; J = 7.68 Hz), 7.39 (t-1H; J=7.88 Hz), 7.69 (d-1H; J =8.50 Hz).

EXAMPLE 71

6-{4-[2-(BENZYL-METHYL-AMINO)-ETHOXY]-2-ISOPROPOXY-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.27 (d-6H; J = 6.02 Hz), 2.34 (s-3H), 2.83 (t-2H; J = 6.01 Hz), 3.61 (s-2H), 4.10 (t-2H; J = 6.02 Hz), 4.41-4.48 (m-3H), 6.36 (d-1H; J = 8.09 Hz), 6.51-6.57 (m-2H), 7.23-7.34 (m-5 H), 7.41 (t-1H; J = 8.09 Hz), 7.70 (d-1H; J = 8.50 Hz).

EXAMPLE 72

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2-METHOXY-5-PROPYL-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.34 (s-6H), 2.74 (t-2H), 3.79 (s-3H), 4.10 (t-2H), 4.49 (bs-2H), 6.38 (dd-1H; J = 8.09 Hz, 0.62 Hz), 6.54-6.58 (m-2H), 7.12 (dd-1H; J = 7.47 Hz, 0.83 Hz), 7.42 (t-1H; J = 7.68 Hz), 7.65 (m-1H).

EXAMPLE 73

6-[5-ALLYL-4-(2-DIMETHYLAMINO-ETHOXY)-2-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.38 (s-6H), 2.80 (t-2H; J = 5.81 Hz), 3.33 (d-2H; J = 6.65 Hz), 3.80 (s-3H), 4.13 (t-2H; J = 5.82 Hz), 4.54 (bs-2H), 4.96-5.06 (m-2H), 5.91-6.00 (m-1H), 6.37 (dd-1H; J = 0.62 Hz; J = 8.10 Hz), 6.50 (s-1H), 7.10 (dd-1H; J = 0.62 Hz; J = 8.31 Hz), 7.41 (t-1H; J = 8.10 Hz), 7.49 (s-1H).

EXAMPLE 74

6-[5-ALLYL-2-METHOXY-4-(2-PYRROLIDIN-1-YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.79-1.82 (m-4H), 2.58-2.68 (m-4H), 2.92-2.96 (m-2H), 3.32-3.34 (m-2H), 3.78 (s-3H), 4.14-4.17 (m-2H), 4.41 (bs-2H), 4.94-5.04 (m-2H), 5.90-6.00 (m-1H), 6.35 (dd-1H; J = 0.83 Hz; J = 7.88 Hz), 6.49 (s-1H), 7.10 (dd-1H; J = 0.83 Hz; J = 7.68 Hz), 7.40 (m-1H), 7.48 (s-1H).

EXAMPLE 75

6-[3-ALLYL-4-(2-DIMETHYLAMINO-ETHOXY)-2-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.38 (s-6H), 2.80 (t-2H; J = 5.81 Hz), 3.45 (s-3H), 3.45-3.47 (m-2H), 4.12 (t-2H; J = 5.81 Hz), 4.47 (bs-2H), 4.92-4.99 (m-2H), 5.94-6.01 (m-1H), 6.40 (d-1H; J = 8.09 Hz), 6.71 (d-1H: J = 8.50 Hz), 7.15 (d-1H; J = 7.47 Hz), 7.44 (t-1H; J = 7.47 Hz), 7.50 (d-1H; J = 8.72 Hz).

The title compounds of Examples 76-94 were prepared using procedures analogous to those described in Examples 1 and 27-30.

EXAMPLE 76

6-[2-METHOXY-4-(PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.92-2.14 (m-3H), 2.85-3.20 (m-3H), 3.79 (s-3H), 4.44 (bs-2H), 4.83-4.86 (m-1H), 6.37 (dd-1H; J = 8.09), 6.47-6.52 (m-2H), 7.12 (d-1H; J = 7.68 Hz), 7.39-7.46 (m-1H), 7.65 (d-1H; J = 8.30 Hz).

EXAMPLE 77

6-[2-METHOXY-4-(1-METHYL-PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR (CDCl$_3$) δ 1.96-2.43 (m-3H), 2.38 (s-3H), 2.73-2.86 (m-3H), 3.78 (s-3H), 4.40 (bs-2H), 4.83-4.89 (m-1H), 6.38 (d-1H; J = 8.09), 6.46-6.51 (m-2H), 7.12 (d-1H; J = 7.47 Hz), 7.39-7.44 (m-1H), 7.63 (d-1H; J = 8.50 Hz).

EXAMPLE 78

6-[2-ETHOXY-4-(PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

Bis HCl salt: ^{1}H NMR (CD$_3$OD) δ 1.39-1.43 (m-3H), 2.33-2.39 (m-2H), 3.46-3.51 (m-1H), 3.57-3.65 (-3H), 4.16 (q-2H), 5.33 (bs-1H), 6.73-6.77 (m-1H), 6.90-6.93 (m-1H), 6.97-7.00 (m-1H), 7.50-7.53 (m-1H), 7.91-7.96 (m-1H).

EXAMPLE 79

6-[2-Isopropoxy-4-(pyrrolidin-3-yloxy)-phenyl]-pyridin-2-ylamine

^{1}H NMR (CDCl$_3$) δ 1.28 (d-6H; J = 6.02 Hz), 1.97-2.13 (m-2H), 2.82-3.23 (m-4H), 4.41-4.48 (m-3H), 4.85(m-1H), 6.38 (d-1H; J = 7.88 Hz), 6.47-6.52 (m-2H), 7.21-7.25 (m-2H), 7.41 (t-1H; J = 7.89 Hz), 7.68 (d-1H; J = 8.50 Hz).

EXAMPLE 80

6-[2-METHOXY-4-(PIPERIDIN-4-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR (CD$_3$OD) δ 2.04-2.20 (m-4H), 3.27-3.39 (m-2H), 3.58-3.61 (m-2H), 3.91 (s-3H), 4.84 (m-1H), 6.80-6.98 (m-4H), 7.48-7.52 (m-1H), 7.83-7.93 (m-1H).

EXAMPLE 81

6-[2-METHOXY-4-(2,2,6,6-TETRAMETHYL-PIPERIDIN-4-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR (CDCl$_3$) δ 1.23-1.38 (m-14H), 2.11-2.15 (m-2H), 3.81 (s-3H), 4.43 (m-1H), 4.70-4.75 (m-1H), 6.40 (d-1H; J = 8.08 Hz), 6.51 (d-1H; J = 2.28 Hz), 6.57 (dd-1H; J = 2.29 Hz; J = 8.51 Hz), 7.14 (d-1H; J = 7.47 Hz), 7.44 (t-1H; J = 7.67 Hz), 7.66 (d-1H; J = 8.50 Hz).

EXAMPLE 82

6-[2-ISOPROPOXY-4-(PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR (CDCl$_3$) δ 1.27 (d-6H; J = 6.01 Hz), 1.93-2.16 (m-2H), 2.85-3.20 (m-4H), 4.41-4.47 (m-3H), 4.81-4.84 (m-1H), 6.36 (dd-1H; J = 0.83 Hz; J = 8.10 Hz), 6.46 (d-1H; J = 2.08 Hz), 6.51 (dd-1H; J = 1.66 Hz; J = 7.90 Hz), 7.21-7.25 (m-1H), 7.37-7.42 (m-1H), 7.69 (d-1H; J = 8.51 Hz).

EXAMPLE 83

3-[4-(6-AMINO-PYRIDIN-2-YL)-3-METHOXY-PHENOXY]-AZETIDINE-1-CARBOXYLIC ACID TERT-BUTYL ESTER

^{1}H NMR ($CDCl_3$) δ 1.43 (s-9H), 3.79 (s-3H), 3.97-4.00 (m-2H), 4.26-4.30 (m-2H), 4.45 (bs-2H), 4.89 (m-1H), 6.28 (dd-1H; J = 2.29 Hz; J = 8.54 Hz), 6.38 (d-1H; J = 8.10 Hz), 6.44 (d-1H; J = 2.28 Hz), 7.10 (d-1H; J = 7.68 Hz), 7.42 (t-1H; J = 7.90 Hz), 7.62 (d-1H; J = 8.51 Hz).

EXAMPLE 84

6-[4-(AZETIDIN-3-YLOXY)-2-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR (CD_3OD) HCl salt: δ 3.93 (s-3H), 4.15-4.19 (m-2H), 4.57-4.62 (m-2H), 5.26-5.29 (m-1H), 6.57 (dd-1H; J = 2.78 Hz; J = 8.50 Hz), 6.72 (d-1H; J = 2.07 Hz),6.89-6.99 (m-2H), 7.52 (dd-1H; J = 2.28 Hz; J = 8.51 Hz), 7.90-7.95 (m-1H).

EXAMPLE 85

6-[2-METHOXY-4-(1-METHYL-AZETIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.41 (s-3H), 3.09-3.14 (m-2H), 3.79 (s-3H), 3.79-3.87 (m-2H), 4.44 (bs-2H), 4.76-4.81 (m-1H), 6.34-6.44 (m-2H), 6.52 (d-1H; J = 2.07 Hz), 7.09-7.12 (m-1H), 7.40-7.44 (m-1H), 7.61-7.65 (m-1H).

EXAMPLE 86

6-[2-ISOPROPOXY-4-(PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.27 (d-6H; J = 6.02 Hz), 2.00-2.15 (m-2H), 3.03-3.26 (m-4H), 3.90 (bs-1H), 4.40-4.47 (m-3H), 4.87 (m-1H), 6.38 (dd-1H; J = 0.83 Hz; J = 8.10 Hz), 6.47 -6.52 (m-2H), 7.20 (dd-1H; J = 0.83 Hz; J = 7.68 Hz), 7.24 (d-1H; J = 1.04 Hz), 7.41 (t-1H; J = 8.10 Hz), 7.67 (d-1H; J = 8.31 Hz).

EXAMPLE 87

6-[2-ISOPROPOXY-4-(PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.25 (d-6H; J = 6.02 Hz), 1.91-2.13 (m-2H), 2.35 (bs-1H), 2.86-3.19 (m-4H), 4.39-4.45 (m-3H), 4.80-4.83 (m-1H), 6.34-6.36 (m-1H), 6.44 (d-1H; J = 2.28 Hz), 6.49 (dd-1H; J = 2.28 Hz; J = 8.51 Hz), 7.19-7.24 (m-1H), 7.36-7.41 (m-1H), 7.67 (dd-1H; J = 3.53 Hz; J = 8.51 Hz).

EXAMPLE 88

6-[2-METHOXY-4-(PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR (CD_3OD) HCl salt: δ 2.00-2.10 (m-1H), 2.15-2.25 (m-1H), 3.21-3.64 (m-5H), 3.94 (s-3H), 5.34 (m-1H), 6.78-7.00 (m-4H), 7.54 (d-1H; J = 8.51 Hz), 7.93 (dd-1H; J = 7.68 Hz; J = 8.39 Hz).

EXAMPLE 89

6-[2-METHOXY-4-(1-METHYL-PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.98-2.03 (m-1H), 2.27-2.44 (m-2H), 2.38 (s-3H), 2.74-2.86 (m-3H), 3.78 (s-3H), 4.45 (bs-2H), 4.82-4.87 (m-1H), 6.36(dd-1H; J = 0.83 Hz; J = 8.09 Hz), 6.45-6.51 (m-2H), 7.11 (dd-1H; J = 0.62 Hz; J = 7.47 Hz), 7.41 (t-1H; J = 7.83 Hz), 7.63 (d-1H; J = 8.30 Hz).

EXAMPLE 90

6-[2-METHOXY-4-(1-METHYL-PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.98-2.03 (m-1H), 2.28-2.44 (m-2H), 2.38 (s-3H), 2.74-2.86 (m-3H), 3.78 (s-3H), 4.43 (bs-2H), 4.84-4.87 (m-1H), 6.37 (dd-1H; J = 0.83 Hz; J = 8.09 Hz), 6.46-6.51 (m-2H), 7.12 (dd-1H; J = 0.83 Hz; J = 7.68 Hz), 7.41 (t-1H; J = 7.68 Hz), 7.63 (d-1H; J = 8.51 Hz).

EXAMPLE 91

6-[2-METHOXY-4-(2-METHYL-2-AZA-BICYCLO[2.2.1]HEPT-5-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.48-1.98 (m-4H), 2.40 (s-3H), 2.61-2.75 (m-2H), 3.05-3.18 (m-2H), 3.80 (s-3H), 4.40 (bs-2H), 4.66-4.70 (m-1H), 6.38 (dd-1H; J = 0.83 Hz; J = 8.09 Hz), 6.50-6.53 (m-2H), 7.13 (dd-1H; J = 0.62 Hz; J = 7.47 Hz), 7.42 (t-1H; J = 7.88 Hz), 7.62-7.64 (m-1H).

EXAMPLE 92

6-[2-METHOXY-4-(1-METHYL-PIPERIDIN-4-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.81-2.03 (m-4H), 2.29 (s-3H), 2.26-2.30 (m-2H), 2.68 (m-2H), 3.79 (s-3H), 4.33-4.43 (m-3H), 6.37 (dd-1H; J = 0.62 Hz; J = 8.10 Hz), 6.51-6.57 (m-2H), 7.11 (dd-1H; J = 0.62 Hz; J = 7.68 Hz), 7.41 (t-1H; J = 7.68 Hz), 7.61 (d-1H; J = 8.52 Hz).

EXAMPLE 93

6-[4-(1-ETHYL-PIPERIDIN-4-YLOXY)-2-METHOXY-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.09 (t-3H; J = 7.26 Hz), 1.80-2.31 (m-6H), 2.41 (q-2H), 2.74 (m-2H), 3.79 (s-3H), 4.33-4.42 (m-3H), 6.36 (d-1H; J = 8.09 Hz), 6.51-6.57 (m-2H), 7.11 (d-1H; J = 7.47 Hz), 7.39-7.43 (m-1H), 7.62 -7.64 (m-1H).

EXAMPLE 94

6-[5-ALLYL-2-METHOXY-4-(1-METHYL-PYRROLIDIN-3-YLOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.02-2.05 (m-1H), 2.29-2.34 (m-1H), 2.42 (s-3H), 2.64-2.74 (m-3H), 3.07-3.11 (m-1H), 3.32-3.34 (m-2H), 3.79 (s-3H), 4.45 (bs-2H), 4.86-4.89 (m-1H), 4.95-5.06 (m-2H), 5.91-5.98 (m-1H), 6.36-6.38 (m-2H), 7.09 (dd-1H; J = 0.83 Hz; J = 7.67 Hz), 7.41 (dd-1H; J = 7.68 Hz; J = 8.09 Hz), 7.48 (s-1H).

The title compounds of Examples 95 - 108 were prepared using procesures analogous to those described in Example 14.

EXAMPLE 95

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2,6-DIMETHYL-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.03 (s-6H), 2.33 (s-6H), 2.73 (t-2H; J = 5.81 Hz), 4.06 (t-2H; J = 5.81 Hz), 4.54 (bs-2H), 6.39 (dd-1H; J = 0.83 Hz; J = 8.30 Hz), 6.51 (dd-1H; J = 0.62 Hz; J = 7.26 Hz), 6.61 (s-2H), 7.41-7.46 (m-1H).

EXAMPLE 96

6-[2,6-DIMETHYL-4-(3-PIPERIDIN-1-YL-PROPOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.45-1.60 (m-2H), 1.68-1.81 (m-4H), 2.08 (s-6H), 2.52-2.85 (m-6H), 4.01 (t-2H), 4.53 (bs-1H), 6.42 (d-1H), 6.53 (d-1H), 6.60 (s-2H), 7.49 (t-1H).

EXAMPLE 97

6-[2,6-DIMETHYL-4-(2-PYRROLIDIN-1-YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.81-1.90 (m-4H), 2.10 (s-6H), 2.66-2.74 (m-4H), 2.96 (t-2H), 4.14(t-2H), 4.52 (bs-1H), 6.42 (d-1H), 6.56(d-1H), 6.65 (s-2H), 7.47 (t-1H).

EXAMPLE 98

6-{2,6-DIMETHYL-4-[3-(4-METHYL-PIPERAZIN-1-YL)-PROPOXY]-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.92-1.99 (m-2H), 2.05 (s-6H), 2.32 (s-3H), 2.52-2.56 (m-6H), 3.99 (t-2H; J = 6.22 Hz), 4.48 (bs-2H), 6.42 (dd-2H; J = 0.83 Hz; J = 8.30 Hz), 6.53 (dd-2H; J = 0.52 Hz; J = 7.26 Hz), 6.61 (s-2H), 7.44-7.48 (m-1H).

EXAMPLE 99

6-[2,6-DIMETHYL-4-(2-MORPHOLIN-4-YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.05 (s-6H), 2.56-2.58 (m-4H), 2.78 (t-2H; J = 5.65 Hz), 3.71-3.74 (m-4H), 4.10 (t-2H; J = 5.60 Hz), 4.54 (bs-2H), 6.41-6.44 (d -1H), 6.53 (d-1H; J = 7.26 Hz), 6.61 (s-2H), 7.44-7.48 (m-1H).

EXAMPLE 100

6-{4-[2-(BENZYL-METHYL-AMINO)-ETHOXY]-2,6-DIMETHYL-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 2.05 (s-6H), 2.33 (s-3H), 2.83 (t-2H; J = 6.01 Hz), 3.63 (s-2H), 4.09 (t-2H; J = 6.01 Hz), 4.49 (bs-2H), 6.42(d-1H), 6.54 (dd-1H; J = 0.62 Hz; J = 7.22 Hz), 6.61 (s-2H), 7.22-7.35 (m-5H), 7.44-7.48 (m-1H).

EXAMPLE 101

2-[4-(6-AMINO-PYRIDIN-2-YL)-3,5-DIMETHYL-PHENOXY]-ACETAMIDE

^{1}H NMR ($CDCl_3$) δ 2.08 (s-6H), 4.49 (s-2H), 4.61 (bs-2H), 5.98 (bs-2H), 6.40-6.60 (m-2H), 6.67 (s-2H), 7.45-7.55 (m-1H).

EXAMPLE 102

6-[4-(2-AMINO-ETHOXY)-2,6-DIMETHYL-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR (CD_3OD) δ 2.02 (s-6H), 3.01 (t-2H; J = 5.18 Hz), 4.00 (t-2H; J = 5.18 Hz), 6.43 (dd-1H; J = 0.83 Hz; J = 7.26 Hz), 6.51 (dd-1H; J = 0.83 Hz; J = 8.52 Hz), 6.67 (s-2H), 7.50 (dd-1H; J = 7.26 Hz; J = 8.52 Hz).

EXAMPLE 103

6-[2-ISOPROPYL-4-(2-PYRROLIDIN-1-YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR **23** (CD_3OD) δ 1.19 (d-6H; J = 6.85 Hz), 2.99 (s-6H), 2.98-3.02 (m-1H), 3.61 (t-2H; J = 4.98 Hz), 4.41 (t-2H; J = 4.77 Hz), 6.68 (d-1H; J = 8.26 Hz), 6.81 (d-1H; J = 8.72 Hz), 6.97 (dd-1H; J = 8.51 Hz; J = 2.49 Hz), 7.09 (d-1H; J = 2.49 Hz), 7.26 (d-1H; J = 8.51 Hz), 7.74-7.78 (m-1H).

EXAMPLE 104

2-(2,5-DIMETHYL-PYRROLIDIN-1-YL)-6-[2-ISOPROPYL-4-(2-PYRROLIDIN-1-YL-ETHOXY)-PHENYL]-PYRIDINE

^{1}H NMR ($CDCl_3$) δ 1.17 (d-6H), 1.29 (d-6H), 1.67-1.82 (m-6H), 2.00-2.05 (m-2H), 2.63-2.66 (m-4H), 2.92 (t-2H), 3.51-3.52 (m-1H), 4.05-4.16 (m-4H), 6.30 (d-1H; J = 8.30 Hz), 6.54 (dd-1H; J = 0.62 Hz: J = 7.25 Hz), 6.74-6.77 (m- 1H), 6.95 (dd-1H; J = 1.04 Hz; J = 2.49 Hz), 7.24-7.27 (m-1H), 7.40-7.44 (m-1H).

EXAMPLE 105

6-{4-[2-(3,5-DIMETHYL-PIPERIDIN-1-YL)-ETHOXY]-2-ISOPROPYL-PHENYL}-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 0.95 (d-6H; J = 6.64 Hz), 1.15 (d-6H; J = 6.84 Hz), 1.16-1.40 (m-4H), 1.50-2.80 (m-6H), 3.17-3.24 (m-1H), 4.09-4.11 (m-2H), 4.43 (bs-2H), 6.43 (dd-1H; J =

2.70 Hz; J = 8.09 Hz), 6.65 (d-1H; J = 7.26 Hz), 6.76 (dd-1H; J = 2.49 Hz; J = 8.30 Hz), 6.89 (d-1H; J = 2.49 Hz), 7.19-7.22 (m-1H), 7.44 (t-1H; J = 7.89 Hz).

EXAMPLE 106

6-[4-(2-DIMETHYLAMINO-ETHOXY)-2-ISOPROPYL-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.12 (d-6H; J = 6.85 Hz), 2.32 (s-6H), 2.72 (t-2H; J = 5.82 Hz), 3.17-3.21 (m-1H), 4.07 (t-2H; J = 5.61 Hz), 4.56 (bs-2H), 6.37 (d-1H; J = 8.10 Hz), 6.61 (d-1H; J = 7.27 Hz), 6.73 (dd-1H; J = 2.70 Hz; J = 8.52 Hz), 6.91 (d-1H; J = 2.70 Hz), 7.18 (d-1H; J = 8.51 Hz), 7.40 (dd-1H; J = 7.27 Hz; J = 7.68 Hz).

EXAMPLE 107

6-[2-TERT-BUTYL-4-(2-DIMETHYLAMINO-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.19 (s-9H), 2.34 (s-6H), 2.73 (t-2H; J = 5.60 Hz), 4.07 (t-2H; J = 5.81 Hz), 4.44 (bs -2H), 6.39 (d-1H; J = 8.09 Hz), 6.61 (d-1H; J = 7.26 Hz), 6.70 (dd-1H; J = 2.70 Hz; J = 8.51 Hz), 6.98 (d-1H; J = 8.51 Hz), 7.07 (d-1H; J = 2.49 Hz), 7.36-7.40 (m-1H).

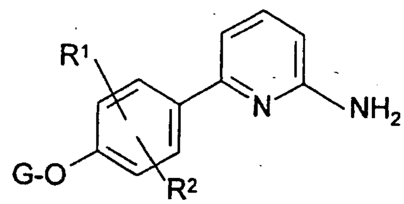
EXAMPLE 108

6-[2-TERT-BUTYL-4-(2-PYRROLIDIN-1-YL-ETHOXY)-PHENYL]-PYRIDIN-2-YLAMINE

^{1}H NMR ($CDCl_3$) δ 1.18 (s-9H), 1.80-1.83 (m-4H), 2.65-2.67 (m-4H), 2.93 (t-2H; J = 5.81 Hz), 4.13 (t-2H; J = 5.81 Hz), 4.47 (bs -2H), 6.38 (d-1H; J = 8.09 Hz), 6.60 (d-1H; J = 7.47 Hz), 6.70 (dd-1H; J = 2.49 Hz; J = 8.30 Hz), 6.98 (d-1H; J = 8.30 Hz), 7.05 (d-1H; J = 2.49 Hz), 7.37 (t-1H; J = 7.68 Hz).

CLAIMS

1. A compound of the formula



wherein R^1 and R^2 are selected, independently, from hydrogen, (C_{1-6})alkyl, $(C_2$-$C_6)$alkenyl, $(C_1$-$C_6)$alkoxy-$(C_1$-$C_3)$alkyl, halo, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$ - $C_7)$alkyl, and $(C_2$ - $C_{10})$alkoxyalkyl; and

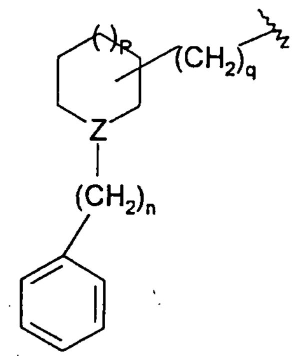
G is selected from hydrogen, aminocarbonyl-$(C_1$-$C_3)$alkyl-, $(C_1$-$C_3)$ alkylaminocarbonyl -$(C_1$-$C_3)$ alkyl-, di-$[(C_1$-$C_3)$alkyl]aminocarbonyl-$(C_1$-$C_3)$ alkyl-, and $N(R^3)(R^4)(C_0$-$C_4)$alkyl-, wherein R^3 and R^4 are selected, independently, from hydrogen, $(C_1$-$C_7)$ alkyl, tetrahydronaphthalene and aralkyl, wherein the aryl moiety of said aralkyl is phenyl or naphthyl and the alkyl moiety is straight or branched and contains from 1 to 6 carbon atoms, and wherein said $(C_1$-$C_7)$ alkyl and said tetrahydronaphthalene and the aryl moiety of said aralkyl may optionally be substituted with from one to three substituents, preferably from zero to two substituents, that are selected, independently, from halo, nitro, hydroxy, cyano, amino, $(C_1$-$C_4)$ alkoxy, and $(C_1$-$C_4)$ alkylamino;

or R^3 and R^4 form, together with the nitrogen to which they are attached, a piperazine, piperidine, azetidine or pyrrolidine ring or a saturated or unsaturated azabicyclic ring system containing from 6 to 14 ring members, from 1 to 3 of which are nitrogen, from zero to two of which are oxygen, and the rest of which are carbon;

and wherein said piperazine, piperidine, azetidine and pyrrolidine rings and said azabicyclic ring systems may optionally be substituted with one or more substituents, preferably with from zero to two substituents, that are selected, independently, from $(C_1$-$C_6)$alkyl, amino, $(C_1$-$C_6)$ alkylamino, [di-$(C_1$-$C_6)$alkyl]amino, phenyl substituted 5 to 6 membered heterocyclic rings containing from 1 to 4 ring nitrogen atoms, benzoyl, benzoylmethyl, benzylcarbonyl, phenylaminocarbonyl, phenylethyl and phenoxycarbonyl, and wherein the phenyl moieties of any of the foregoing substituents may optionally be substituted with one or more substituents, preferably with from zero to two substituents, that are selected, independently, from halo, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy, nitro, amino, cyano, CF_3 and OCF_3;

and wherein said piperazine, piperidine, azetidine and pyrrolidine rings and said azabicyclic ring systems may be attached to -(C_0-C_4)alkyl-O- (wherein the oxygen of said -(C_0-C_4)alkyl-O- is the oxygen atom depicted in structural formula I) at a nitrogen atom of the NR^3R^4 ring or any other atom of the ring having an available bonding site;

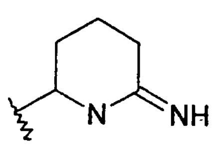
or G is a group of the formula A



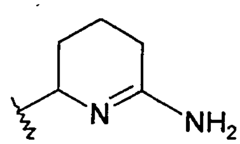
(A)

wherein Z is nitrogen or CH, n is zero or one, q is zero, one, two or three and p is zero, one or two;

and wherein the 2-amino piperidine ring depicted in structure I above may optionally be replaced with



or



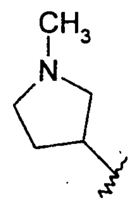
;

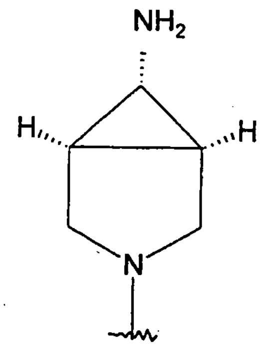
or a pharmaceutically acceptable salt of such compound

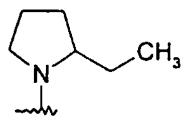
2. A compound according to claim 1, wherein G is NR^3R^4(C_0-C_4)alkyl and NR^3R^4 is a piperidine, piperazine or pyrrolidine ring.

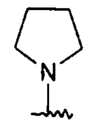
3. A compound according to claim 1 wherein R^1 and R^2 are selected from hydrogen and (C_1-C_2)alkyl.

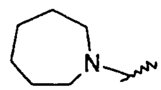
4. A compound according to claim 1 wherein G is $NR^3R^4(C_0\text{-}C_4)$alkyl and NR^3R^4 is a group of the formula

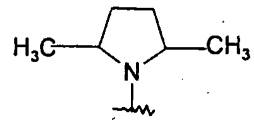


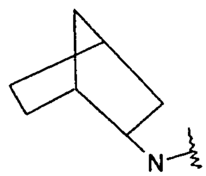


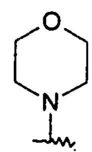


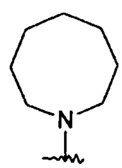


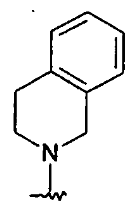


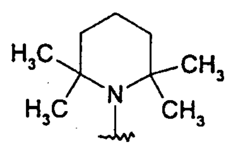


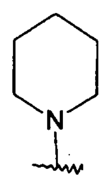


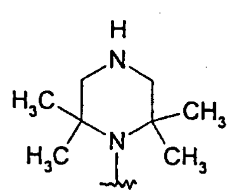




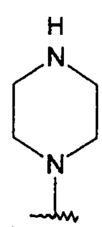








or



5. A compound according to claim 1 wherein G is a group of the formula A and Z is nitrogen.

6. A compound according to claim 1 wherein G is a group of the formula A, Z is nitrogen, each of n and p is one and q is two.

7. A pharmaceutical composition for treating or preventing a condition selected from the group consisting of migraine inflammatory diseases, stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addictions, emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic nephsopathy and cancer in a mammal, comprising an amount of a compound according to claim 1 that is effective in treating or preventing such condition and a pharmaceutically acceptable carrier.

8. A method of treating or preventing a condition selected from the group consisting of migraine inflammatory diseases, stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addictions, emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic nephropathy and cancer in a mammal, comprising administering to said mammal an amount of a compound according to claim 1, that is effective in treating or preventing such condition.

9. A pharmaceutical composition for inhibiting nitric oxide synthase (NOS) in a mammal, according to claim 1, comprising a NOS inhibiting effective amount of a compound according to claim 1, and a pharmaceutically acceptable carrier.

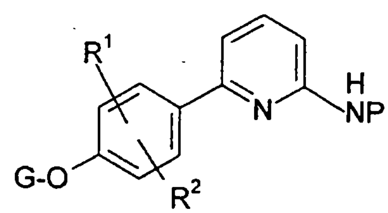
10. A method of inhibiting NOS in a mammal, comprising administering to said mammal a NOS inhibiting effective amount of a compound according to claim 1.

11. A pharmaceutical composition for treating or preventing a condition selected from the group consisting of migraine, inflammatory diseases, stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addictions, emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced

tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic nephrosopathy and cancer in a mammal, comprising a NOS inhibiting effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

12. A method of treating or preventing a condition selected from the group consisting of migraine, inflammatory diseases, stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addictions, emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic nephrosopathy and cancer in a mammal, comprising administering to said mammal a NOS inhibiting effective amount of a compound according to claim 1.

13. A compound of the formula



VIIA

wherein R^1 and R^2 are selected, independently, from hydrogen, halo, hydroxy, (C_1-C_6)alkoxy, (C_1-C_7)alkyl, (C_2-C_6)alkenyl, and (C_2 - C_{10})alkoxyalkyl; and

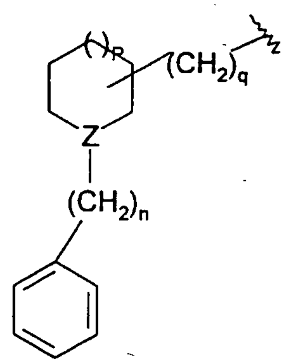
G is selected from hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_3)alkyl, aminocarbonyl-(C_1-C_3)alkyl-, (C_1-C_3) alkylaminocarbonyl -(C_1-C_3) alkyl-, di-[(C_1-C_3)alkyl]aminocarbonyl-(C_1-C_3)alkyl-, and $N(R^3)(R^4)$(C_0-C_4)alkyl-, wherein R^3 and R^4 are selected, independently, from hydrogen, (C_1-C_7) alkyl, tetrahydronaphthalene and aralkyl, wherein the aryl moiety of said aralkyl is phenyl or naphthyl and the alkyl moiety is straight or branched and contains from 1 to 6 carbon atoms, and wherein said (C_1-C_7) alkyl and said tetrahydronaphthalene and the aryl moiety of said aralkyl may optionally be substituted with from one to three substituents, preferably from zero to two substituents, that are selected, independently, from halo, nitro, hydroxy, cyano, amino, (C_1-C_4) alkoxy, and (C_1-C_4) alkylamino;

or R^3 and R^4 form, together with the nitrogen to which they are attached, a piperazine, piperidine, azetidine or pyrrolidine ring or a saturated or unsaturated azabicyclic ring system containing from 6 to 14 ring members, from 1 to 3 of which are nitrogen, from zero to two of which are oxygen, and the rest of which are carbon;

and wherein said piperazine, piperidine, azetidine and pyrrolidine rings and said azabicyclic ring systems may optionally be substituted with one or more substituents, preferably with from zero to two substituents, that are selected, independently, from (C_1-C_6)alkyl, amino, (C_1-C_6) alkylamino, [di-(C_1-C_6)alkyl]amino, phenyl substituted 5 to 6 membered heterocyclic rings containing from 1 to 4 ring nitrogen atoms, benzoyl, benzoylmethyl, benzylcarbonyl, phenylaminocarbonyl, phenylethyl and phenoxycarbonyl, and wherein the phenyl moieties of any of the foregoing substituents may optionally be substituted with one or more substituents, preferably with from zero to two substituents, that are selected, independently, from halo, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, nitro, amino, cyano, CF_3 and OCF_3;

and wherein said piperazine, piperidine, azetidine and pyrrolidine rings and said azabicyclic ring systems may be attached to $-(C_0-C_4)$alkyl-O- (wherein the oxygen of said $-(C_0-C_4)$alkyl-O- is the oxygen atom depicted in structural formula I) at a nitrogen atom of the NR^3R^4 ring or at any other atom of such ring having an available bonding site;

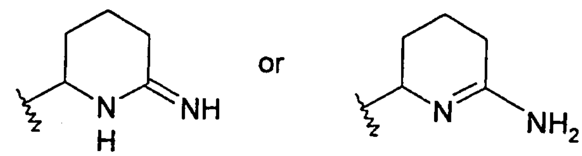
or G is a group of the formula A



(A)

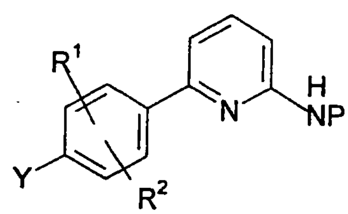
wherein Z is nitrogen or CH, n is zero or one, q is zero, one, two or three and p is zero, one or two;

and wherein the 2-amino piperidine ring depicted in structure I above may optionally be replaced with



and P is a nitrogen protecting group such as trityl, acetyl, benzoyl, trimethylacetyl, t-butoxycarbonyl, benzyloxycarbonyl, or another appropriate nitrogen protecting group, and wherein P can form a ring with the protected nitrogen, in which case the hydrogen that is depicted in formula I above as being attached to such nitrogen is absent.

14. A compound of the formula



wherein Y is fluoro or benzyloxy;

R^1 and R^2 are selected, independently, from hydrogen, halo, hydroxy, (C_1-C_6)alkoxy, (C_1-C_7)alkyl, (C_2-C_6)alkenyl, and (C_2 - C_{10})alkoxyalkyl; and

and P is a nitrogen protecting group such as trityl, acetyl, benzoyl, trimethylacetyl, t-butoxycarbonyl, benzyloxycarbonyl, or another appropriate nitrogen protecting group, and wherein P can form a ring with the protected nitrogen, in which case the hydrogen that is depicted above as being attached to such nitrogen is absent.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 98/00112

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/73 A61K31/44 C07D401/12 //(C07D401/12,213:00, 207:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 97 36871 A (PFIZER (US)) 9 October 1997 see claim 1	1-14
Y	WO 96 18616 A (MERCK & CO INC) 20 June 1996 see page 25-28; claim 1	1-14
Y	WO 95 11231 A (SEARLE & CO) 27 April 1995 see page 200-205; claim 1	1-14
A	WO 94 14780 A (WELLCOME FOUND) 7 July 1994 see page 23-27; claim 1	1-14
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
2 April 1998	24.04.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lauro, P

Form PCT/ISA/210 (second sheet) (July 1992)

Intern: al Application No
PCT/IB 98/00112

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HUSSAINI F A ET AL: "SYNTHESIS OF SUBSTITUTED 2-AMINOPYRIDINES: A VERSATILE APPROACH" JOURNAL OF CHEMICAL RESEARCH. SYNOPSES, no. 3, 1 January 1994, page 86 XP000566748 see examples 4A,4D -----	1,14

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Information on patent family members

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